



US009072758B2

(12) **United States Patent**
Okano et al.

(10) **Patent No.:** **US 9,072,758 B2**
(45) **Date of Patent:** **Jul. 7, 2015**

(54) **CYCLIC AMIDE DERIVATIVE**

(75) Inventors: **Akihiro Okano**, Tokyo (JP); **Munetaka Ohkouchi**, Tokyo (JP); **Muneyoshi Makabe**, Tokyo (JP)

(73) Assignee: **MOCHIDA PHARMACEUTICAL CO., LTD.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/114,017**

(22) PCT Filed: **Apr. 11, 2012**

(86) PCT No.: **PCT/JP2012/059915**

§ 371 (c)(1),
(2), (4) Date: **Oct. 25, 2013**

(87) PCT Pub. No.: **WO2012/147516**

PCT Pub. Date: **Nov. 1, 2012**

(65) **Prior Publication Data**

US 2014/0057871 A1 Feb. 27, 2014

(30) **Foreign Application Priority Data**

Apr. 28, 2011 (JP) 2011-102535
Aug. 26, 2011 (JP) 2011-185340
Oct. 11, 2011 (WO) PCT/JP2011/073355
Feb. 29, 2012 (JP) 2012-044857

(51) **Int. Cl.**

C07D 279/02 (2006.01)
C07D 285/10 (2006.01)
C07D 285/16 (2006.01)
C07D 417/12 (2006.01)
C07D 417/14 (2006.01)
A61K 31/69 (2006.01)
A61K 31/425 (2006.01)
A61K 31/4439 (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC **A61K 31/69** (2013.01); **C07D 417/12** (2013.01); **C07D 417/14** (2013.01); **C07D 279/02** (2013.01); **C07D 285/10** (2013.01); **C07D 285/16** (2013.01); **A61K 31/425** (2013.01); **A61K 31/4439** (2013.01); **A61K 31/54** (2013.01); **A61K 31/541** (2013.01); **A61K 31/549** (2013.01); **A61K 45/06** (2013.01); **C07D 275/03** (2013.01); **C07F 5/04** (2013.01); **A61K 9/145** (2013.01); **A61K 9/1652** (2013.01); **A61K 9/2018** (2013.01); **A61K 9/485** (2013.01)

(58) **Field of Classification Search**

CPC .. **C07D 279/02**; **C07D 285/10**; **C07D 285/16**;
C07D 417/12; **C07D 417/14**
USPC **544/56**; **514/222.2**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2006/0100261 A1 5/2006 Hamamura et al.
2006/0258722 A1 11/2006 Yasuma et al.

(Continued)

FOREIGN PATENT DOCUMENTS

JP 2005-15461 A 1/2005
JP 2005-535568 A 11/2005

(Continued)

OTHER PUBLICATIONS

International Search Report for PCT/JP2012/059915 dated Jun. 19, 2012.

(Continued)

Primary Examiner — Bruck Kifle

(74) Attorney, Agent, or Firm — Birch, Stewart, Kolasch & Birch, LLP

(57)

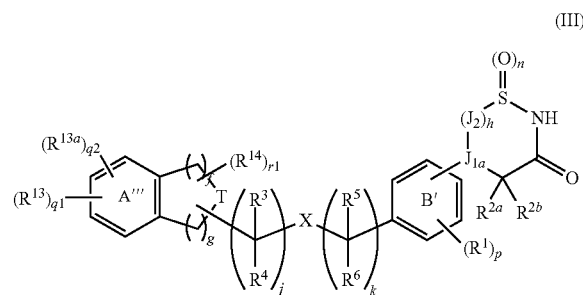
ABSTRACT

[Problem]

To provide a GPR40 activating agent having, as an active ingredient, a novel compound having a GPR40 agonist action, a salt of the compound, a solvate of the salt or the compound, or the like, particularly, an insulin secretagogues and a prophylactic and/or therapeutic agent against diabetes, obesity, or the like.

[Means of solving the problem]

A compound of Formula (III):



(where f is 0 to 2; g is 1 to 4; j is 0 to 3; k is 0 to 2; n is 0 to 2; p is 0 to 4; h is 0 to 3; q1 is 0 to 3; q2 is 0 or 1; r1 is 0 to 2 (with the proviso that q1+q2+r1 is 0 to 5); J1a is —CR^{11a}—, N; J2 is —CR^{12a}R^{12b}—, —CR^{12c}—; T is —CH₂—, O, —S(O)_i— (i is an integer of 0 to 2) or —NR⁷—; X is O, S, or —NR⁷—; ring A''' is a benzene ring, a pyridine ring; ring B' is a benzene ring, a pyridine ring, a pyrimidine ring; and R¹ to R¹⁴ are specific groups),

a salt of the compound, or a solvate of the salt or the compound.

14 Claims, No Drawings

(51) **Int. Cl.**

A61K 31/54 (2006.01)
A61K 31/541 (2006.01)
A61K 31/549 (2006.01)
A61K 45/06 (2006.01)
C07D 275/03 (2006.01)
C07F 5/04 (2006.01)
A61K 9/14 (2006.01)
A61K 9/16 (2006.01)
A61K 9/20 (2006.01)
A61K 9/48 (2006.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

2008/0139576 A1 6/2008 Coppola et al.
 2009/0012093 A1 1/2009 Fukatsu et al.
 2009/0170908 A1 7/2009 Shimada et al.
 2009/0181928 A1 7/2009 Neubert et al.
 2009/0186909 A1 7/2009 Negoro et al.
 2010/0130599 A1 5/2010 Coty et al.
 2010/0261645 A1 10/2010 DeFossa et al.
 2010/0267775 A1 10/2010 Negoro et al.
 2011/0065739 A1 3/2011 Ishikawa et al.
 2012/0157459 A1 6/2012 Okano et al.
 2012/0220772 A1 8/2012 Okano et al.
 2012/0277150 A1 11/2012 Ohkouchi
 2013/0203739 A1 8/2013 Okano et al.

FOREIGN PATENT DOCUMENTS

JP 2009-532379 A 9/2009
 WO WO 00/42029 A1 7/2000
 WO WO 03/082841 A1 10/2003
 WO WO 2004/011446 A1 2/2004
 WO WO 2004/022551 A1 3/2004
 WO WO 2004/041266 A1 5/2004
 WO WO 2005/035551 A2 4/2005
 WO WO 2005/051890 A1 6/2005
 WO WO 2005/063729 A1 7/2005
 WO WO 2005/086661 A2 9/2005
 WO WO 2007/033002 A1 3/2007
 WO WO 2007/067612 A1 6/2007

WO WO 2007/067613 A1 6/2007
 WO WO 2007/067614 A1 6/2007
 WO WO 2007/089857 A2 8/2007
 WO WO 2007/115058 A2 10/2007
 WO WO 2007/123225 A1 11/2007
 WO WO 2008/001931 A2 1/2008
 WO WO 2008/022771 A1 2/2008
 WO WO 2008/030520 A1 3/2008
 WO WO 2008/033931 A1 3/2008
 WO WO 2008/066131 A1 6/2008
 WO WO 2006/130514 A1 10/2008
 WO WO 2009/039945 A1 4/2009
 WO WO 2009/048527 A1 4/2009
 WO WO 2009/054390 A1 4/2009
 WO WO 2009/054423 A1 4/2009
 WO WO 2009/054479 A1 4/2009
 WO WO 2009/109999 A1 9/2009
 WO WO 2009/111056 A1 9/2009
 WO WO 2009/147990 A1 12/2009
 WO WO 2010/091176 A1 6/2010
 WO WO 2010/085525 A1 7/2010
 WO WO 2010/143733 A1 12/2010
 WO WO 2011/046851 A1 4/2011
 WO WO 2011/052756 A1 5/2011
 WO WO 2011/066183 A1 6/2011
 WO WO 2011/078371 A1 6/2011
 WO WO 2012/046869 A1 4/2012
 WO WO 2012/147516 A1 11/2012
 WO WO 2012/147616 A1 11/2012

OTHER PUBLICATIONS

Campbell, A. D. and A. M. Birch, "Expedient Synthesis of Sulfonylhydantoins and Two Six-Membered Analogues," Synlett (2005), No. 5, pp. 0834-0838

Chiasson of et al., "Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients with Impaired Glucose Tolerance: The Stop-NIDDM Trial," JAMA (2003), vol. 290, No. 4: pp. 486-494

Itoh et al., "Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40," Nature (Mar. 13, 2003), vol. 422, pp. 173-176.

Kotarsky et al., "A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs," Biochemical and Biophysical Research Communications (2003), vol. 301, pp. 406-410.

Extended European Search Report dated Oct. 29, 2014 for Application No. 12777792.8.

CYCLIC AMIDE DERIVATIVE

TECHNICAL FIELD

The present invention relates to a compound for modulating the functions of G protein-coupled receptor 40 (GPR40). In particular, the present invention relates to a compound characterized by having a saturated cyclic amide structure having $-\text{S}(\text{O})-$, $-\text{NH}-\text{CO}-$ (n is an integer of 0 to 2) bonded to a ring B (hereinafter, called the cyclic amide structure) of Formula (I), a salt of the compound, a solvate of the compound or the salt, a pharmaceutical composition containing the compound as an active ingredient, prophylactic and/or therapeutic agents against GPR40-involving diseases, especially diabetes, and an insulin secretagogue.

BACKGROUND ART

Diabetes is categorized into Type 1 diabetes (insulin-dependent diabetes) and Type 2 diabetes (non-insulin-dependent diabetes), and borderline type diabetes (glucose tolerance disorders) has also attracted attention as a pre-diabetic condition in recent years. Type 1 diabetes is characterized by a partial or complete inability to produce insulin, which is a blood glucose regulating hormone. Type 2 diabetes is characterized by induced peripheral insulin resistance and impaired insulin secretion. Borderline type diabetes is a pathological condition exhibiting impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), associated with a risk of developing Type 2 diabetes or diabetes complications.

Diabetes is caused by several predisposing factors. It is a disease characterized by high glucose levels in blood plasma in fasting and postprandial states or during an oral glucose tolerance test or by chronic hyperglycemia, in general. Controlling chronic hyperglycemia is essential in clinical management and treatment of diabetes. In particular, reduced insulin secretion from beta cells of the pancreas can induce an abrupt increase in postprandial blood glucose levels in Type 2 diabetes or borderline type diabetes. An international large-scale clinical trial has revealed that it is essential to control postprandial hyperglycemia in impaired glucose tolerance for suppressing the development and progress of not only diabetes but also hypertension and cardiovascular diseases (JAMA, 290, 486-494 (2003) (Non-Patent Document 1)). On the basis of these findings, the International Diabetes Federation published new guidelines for diabetes treatment (postprandial blood glucose control guidelines) in 2007, which recommend control of postprandial blood glucose levels as essential for Type 1 and 2 diabetic patients to alleviate diabetes and reduce risk of complications. As a practical step, an increased administration of an alpha-glucosidase inhibitor (voglibose) that is a drug for alleviating excessive postprandial blood glucose levels associated with diabetes, has been approved in Japan as a prophylactic agent against diabetes, aiming to "inhibit the development of Type 2 diabetes from impaired glucose tolerance". As described above, there has been increasing awareness of the needs of nonpharmacological and pharmacological treatments against diabetes and borderline type diabetes, targeting the control of postprandial blood glucose levels in recent years.

Diabetes is treated mainly through diet regulation and exercise. When these fail to alleviate symptoms, pharmacological treatment is needed. Various types of drugs are available as prophylactic or therapeutic agents against diabetes. Among them, examples of insulin secretagogues include sulfonylurea agents (e.g., glibenclamide, glimepiride) and rapid-acting insulin secretagogues (e.g., nateglinide, mitiglinide), all of

which stimulate beta cells of the pancreas so as to accelerate insulin secretion. These drugs are, however, known for their ineffectiveness (primary failure, secondary failure) and side effects such as induced hypoglycemic effects. Analogs (e.g., exenatide, liraglutide) of glucagon-like peptide-1 (GLP-1), which are hormones accelerating glucose-responsive insulin secretion in beta cells of the pancreas, have become available as novel insulin secretagogues, but they are administered by injection and known for their side effects of transient gastrointestinal tract disorders. Other examples of insulin secretagogues include dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin, vildagliptin, alogliptin), which inhibit the degradation of intrinsic GLP-1, but they are known for their side effects of epipharyngitis, headache, and infections. Alpha-glucosidase inhibitors (e.g., acarbose, voglibose) inhibit the degradation and digestion of carbohydrate and thus limit an abrupt increase in postprandial blood glucose levels, but they need to be taken immediately before meals and are known for their side effects such as distension and diarrhea and serious liver disorders. Biguanides (e.g., metformin, buformin) are insulin resistance improving agents enhancing insulin sensitivity and thereby alleviating hyperglycemia, but are known to potentially induce side effects such as lactic acidosis, nausea, and vomiting. Thiazolidinedione derivatives (e.g., pioglitazone, rosiglitazone) are peroxisome proliferator-activated receptor (PPAR) gamma agonists. The derivatives increase insulin sensitivity in adipose tissue, the liver, and skeletal muscles and thereby alleviate chronic hyperglycemia, but are known to cause edema, weight gain, and serious side effects of liver disorders. Side effects of these drugs do not always occur, but remain as a major obstacle to high satisfaction with treatment. Therefore, the demand has been increasing for insulin secretagogues, particularly orally administrable insulin secretagogues, entailing few issues and side effects caused by conventional prophylactic and therapeutic agents as described above and inhibiting postprandial hyperglycemia without inducing hypoglycemia.

Fatty acid plays an important role in insulin use in the liver and skeletal muscles, glucose-responsive insulin secretion from the pancreas, and inflammation associated with fat accumulation in adipose tissue. A strong correlation is known between increased levels of fatty acid in blood plasma and the development of diabetes, metabolic syndrome, obesity, and adiposity.

GPR40, one of the G-protein-coupled receptors, is categorized in the free fatty acid receptor (FFAR) family and activated by C_{6-22} saturated or unsaturated fatty acid. It is disclosed that high expression of GPR40 is observed in beta cells of the pancreas where the receptor is involved in insulin secretion caused by fatty acid (Nature, 422, 173-176 (2003) (Non-Patent Document 2)). Non-fatty-acid low-molecular-weight compounds having a GPR40 agonist action have been found in recent years, and it is disclosed that thiazolidinediones, which are insulin sensitivity improving agents, and MEDICA 16, which is a hypolipidemic agent, also exhibit agonist actions (Biochem. Biophys. Res. Comm., 301, 406-410 (2003) (Non-Patent Document 3)).

In the pancreatic islets of Langerhans isolated from GPR40 knockout mice, the glucose-responsive insulin secretagogue action of fatty acid is lower than the case with normal mice. Accordingly, substances having a GPR40 agonist action like fatty acid are expected to have the effect of inhibiting postprandial hyperglycemia based on the glucose-responsive insulin secretagogue action in the pancreas. Therefore, substances having a GPR40 agonist action are considered to be effective as prophylactic and therapeutic agents against diabetes or borderline type diabetes.

Studies have been progressed on compounds having a GPR40 activating action as insulin secretagogues or therapeutic agents against diabetes. Technologies related to compounds having a GPR40 agonist action are disclosed, for example, in WO 2004/041266 pamphlet (Patent Document 1), WO 2005/086661 pamphlet (Patent Document 2), WO 2007/123225 pamphlet (Patent Document 3), WO 2008/001931 pamphlet (Patent Document 4), WO 2009/054390 pamphlet (Patent Document 5), WO 2009/054423 pamphlet (Patent Document 6), WO 2009/054479 pamphlet (Patent Document 7), WO 2011/046851 pamphlet (Patent Document 8), WO 2010/143733 pamphlet (Patent Document 9), WO 2007/033002 pamphlet (Patent Document 10), WO 2009/048527 pamphlet (Patent Document 11), WO 2009/111056 pamphlet (Patent Document 12), WO 2005/051890 pamphlet (Patent Document 13), WO 2004/022551 pamphlet (Patent Document 14), WO 2004/011446 pamphlet (Patent Document 15), WO 2008/030520 pamphlet (Patent Document 16), WO 2011/066183 pamphlet (Patent Document 17), WO 2010/091176 pamphlet (Patent Document 18), WO 2010/085525 pamphlet (Patent Document 19), WO 2009/039943 pamphlet (Patent Document 20), WO 2005/063729 pamphlet (Patent Document 21), and WO 2008/130514 pamphlet (Patent Document 22). These documents, however, do not disclose or suggest any compounds having a saturated cyclic amide structure bonded to a benzene ring or the like.

A technique related to a compound having a 5-aryl-3-isothiazolidinone ring is disclosed in WO 2005/035551 pamphlet (Patent Document 23). The compound disclosed in Patent Document 23, however, is a compound having an inhibitory effect on protein tyrosine phosphatase 1B (PTP1B), and its structure of a linker moiety is fundamentally different from that of the compounds according to the present invention. Another compound group having a 5-aryl-3-isothiazolidinone ring is disclosed in WO 2008/033931 pamphlet (Patent Document 24) as a compound having an inhibitory effect on PTP 1B. The compound disclosed in Patent Document 24, however, has a fundamental framework different from that of the compounds according to the present invention.

Techniques related to compounds having a 5-aryl-1,2,5-thiadiazolidin-3-one ring are disclosed in WO 2003/082841 pamphlet (Patent Document 25), WO 2005/035551 pamphlet (Patent Document 24), WO 2007/067612 pamphlet (Patent Document 26), WO 2007/067613 pamphlet (Patent Document 27), WO 2007/067614 pamphlet (Patent Document 28), WO 2007/089857 pamphlet (Patent Document 29), WO 2007/115058 pamphlet (Patent Document 30), and WO 2009/109999 pamphlet (Patent Document 31).

The compounds disclosed in Patent Documents 24 to 31, however, are compounds having an inhibitory effect on PTP1B, and their fundamental structures of linker moieties are different from that of the compounds according to the present invention.

The compound having a 5-aryl-1,2,5-thiadiazolidin-3-one ring is also disclosed in WO 2008/022771 pamphlet (Patent Document 32). The compound disclosed in Patent Document 32, however, is a compound having an inhibitory effect on sphingomyelin and having an amide structure on its linker moiety, and is different from that of the compounds according to the present invention.

A technique related to the compound having a 5-aryl-1,2,6-thiadiazinan-3-one ring and a 5-aryl-1,2-thiazinan-3-one ring is disclosed in Synlett, 834-838 (2005) (Non-Patent Document 4). The compound disclosed in Non-Patent Document 4, however, has a fundamental framework different from that of the compounds according to the present inven-

tion and does not disclose or suggest any compounds having a GPR40 agonist action like the present invention.

WO 2008/066131 pamphlet (Patent Document 33) and WO 2009/147990 pamphlet (Patent Document 34) disclose compounds having a 3-hydroxy-5-arylisoaxazolyl group as compounds having a G protein-coupled receptor 120 (GPR120) agonist action. These documents, however, do not disclose or suggest any compounds having a GPR40 agonist action or a saturated cyclic amide structure bonded to a benzene ring or the like as in the present invention.

WO 2011/052756 pamphlet (Patent Document 35) and WO 2011/078371 pamphlet (Patent Document 36) have recently disclosed compounds having a 3-hydroxy-5-arylisoaxazole group or a 3-hydroxy-5-arylisothiazazole group as compounds having a GPR40 activating action.

In the development of drugs, various strict criteria must be met in terms of absorption, distribution, metabolism, excretion, and other factors as well as targeted pharmacological actions. There are various things to consider, for example, interaction with other drugs, desensitization or durability, digestive tract absorption after oral administration, speed to reach the small intestine, absorption speed and first pass effect, organ barriers, protein binding, drug metabolizing enzyme induction or inhibition, excretion route and clearance in the body, and application methods (application sites, methods, purposes). It is difficult to find a drug that meets all the criteria.

Several compounds are reported to have a GPR40 agonist action, but none of them has been marketed so far. Such agonists could also involve the above-mentioned general issues in the development phase of drugs. More specifically, they have problems in usefulness and safety, such as low metabolism stability and difficulty in systemic exposure by oral administration, unfavorable pharmacokinetic effects including absorption and persistence properties, an activity of inhibiting the human ether-a-go-go related gene (hERG) channel, possibly resulting in arrhythmia, an activity of inducing or inhibiting drug metabolizing enzymes (e.g., cytochrome P450), or side effects caused by CNS from penetration through blood-brain barrier. Therefore, required is a compound that solves these issues as much as possible and still has high efficacy.

Moreover, required as a GPR40 agonist is a compound with fewer issues or side effects as described above than the aforementioned conventional drugs that have been used to prevent or treat diabetes (particularly Type 2 diabetes or borderline type diabetes).

PRIOR ART DOCUMENTS

Patent Documents

Patent Document 1: WO 2004/041266 pamphlet
 Patent Document 2: WO 2005/086661 pamphlet
 Patent Document 3: WO 2007/123225 pamphlet
 Patent Document 4: WO 2008/001931 pamphlet
 Patent Document 5: WO 2009/054390 pamphlet
 Patent Document 6: WO 2009/054423 pamphlet
 Patent Document 7: WO 2009/054479 pamphlet
 Patent Document 8: WO 2011/046851 pamphlet
 Patent Document 9: WO 2010/143733 pamphlet
 Patent Document 10: WO 2007/033002 pamphlet
 Patent Document 11: WO 2009/048527 pamphlet
 Patent Document 12: WO 2009/111056 pamphlet
 Patent Document 13: WO 2005/051890 pamphlet
 Patent Document 14: WO 2004/022551 pamphlet
 Patent Document 15: WO 2004/011446 pamphlet

5

Patent Document 16: WO 2008/030520 pamphlet
 Patent Document 17: WO 2011/066183 pamphlet
 Patent Document 18: WO 2010/091176 pamphlet
 Patent Document 19: WO 2010/085525 pamphlet
 Patent Document 20: WO 2009/039943 pamphlet
 Patent Document 21: WO 2005/063729 pamphlet
 Patent Document 22: WO 2008/130514 pamphlet
 Patent Document 23: WO 2005/035551 pamphlet
 Patent Document 24: WO 2008/033931 pamphlet
 Patent Document 25: WO 2003/082841 pamphlet
 Patent Document 26: WO 2007/067612 pamphlet
 Patent Document 27: WO 2007/067613 pamphlet
 Patent Document 28: WO 2007/067614 pamphlet
 Patent Document 29: WO 2007/089857 pamphlet
 Patent Document 30: WO 2007/115058 pamphlet
 Patent Document 31: WO 2009/109999 pamphlet
 Patent Document 32: WO 2008/022771 pamphlet
 Patent Document 33: WO 2008/066131 pamphlet
 Patent Document 34: WO 2009/147990 pamphlet
 Patent Document 35: WO 2011/052756 pamphlet
 Patent Document 36: WO 2011/078371 pamphlet

Non-Patent Documents

Non-Patent Document 1: JAMA, 290, 486-494 (2003)
 Non-Patent Document 2: Nature, 422, 173-176 (2003)
 Non-Patent Document 3: Biochem. Biophys. Res. Comm.,
 301, 406-410 (2003)
 Non-Patent Document 4: Synlett, 834-838 (2005)

SUMMARY OF THE INVENTION

Problem to be Solved by the Invention

In view of such medical circumstances related to diabetes, prophylactic and therapeutic drugs are required that accelerate insulin secretion, particularly glucose-responsive insulin secretion, through activation of GPR40, and thus exhibit the action of lowering blood glucose levels, particularly inhibiting postprandial hyperglycemia.

Particularly required are orally administrable GPR40 activating agents, insulin secretagogues, prophylactic and/or therapeutic agents against GPR40-involving diseases (particularly prophylactic and/or therapeutic agents against diabetes or obesity) all of which have high safety, excellent efficacy, and high selectivity with respect to other members of the FFAR family or similar receptors.

In particular, there are issues to be addressed as issues with the conventional techniques described above. More specifically, there are the following issues to be addressed with prophylactic and therapeutic agents against diabetes: ineffectiveness (primary failure, secondary failure) and side effects such as induced hypoglycemic effects caused by sulfonylurea agents and rapid-acting insulin secretagogues; transient gastrointestinal tract disorders caused by GLP-1 analogs; side effects of epipharyngitis, headache, and infections caused by DPP-IV inhibitors; side effects such as distension and diarrhea and serious liver disorders caused by alpha-glucosidase inhibitors; side effects such as lactic acidosis, nausea, and vomiting caused by biguanides; edema, weight gain, and serious liver disorders caused by thiazolidinedione derivatives; and so on. Other issues to be addressed include solubility, improvement in metabolism stability, enhancement of absorption properties, improvement in pharmacokinetic effects, reduction in the activity of inhibiting hERG, reduction in the activity of inducing or inhibiting drug metabolizing enzymes (e.g., cytochrome P450), and reduction in central

6

penetration. Consequently, there are needs for insulin secretagogues and prophylactic and/or therapeutic agents against GPR40-involving diseases (particularly prophylactic and/or therapeutic agents against diabetes or obesity) all of which solve at least one of the issues, to be orally administrable to mammals including human beings, and clinically usable in particular.

Means for Solving the Problem

As a result of assiduous research for solving the above problems by obtaining a compound having high safety and/or excellent efficacy and modulating the functions of GPR40, the inventors of the present invention have found that a derivative having a cyclic amide structure of Formula (I) has a GPR40 agonist action. The compound of the present invention has an excellent glucose-responsive insulin secretagogue action and has a strong hyperglycemia-inhibiting action during glucose load.

Effects of the Invention

The present invention provides: a compound characterized by having a cyclic amide structure of Formula (I), a salt of the compound, or a solvate of the compound or the salt; and a pharmaceutical composition characterized by containing as an active ingredient, the compound, a pharmaceutically acceptable salt of the compound, or a solvate of the compound or the pharmaceutically acceptable salt.

The compound of the present invention is a compound having a GPR40 agonist action, or a compound having an action of lowering a blood glucose level, particularly an action of inhibiting postprandial hyperglycemia, by activating GPR40 to accelerate an insulin secretion, particularly a glucose-responsive insulin secretion. The pharmaceutical composition containing the compound of the present invention as an active ingredient can be orally administrated and is expected as an insulin secretagogue or a prophylactic agent and/or a therapeutic agent for a GPR40-involving disease, particularly diabetes (particularly Type 2 diabetes or borderline type diabetes) or obesity and adiposity.

The group of the compounds of the present invention has at least one of characteristics such as having advantageous solubility, having high metabolism stability, having excellent oral absorption properties, having a small activity of inhibiting the hERG channel, and having small central penetration, and thus is highly useful.

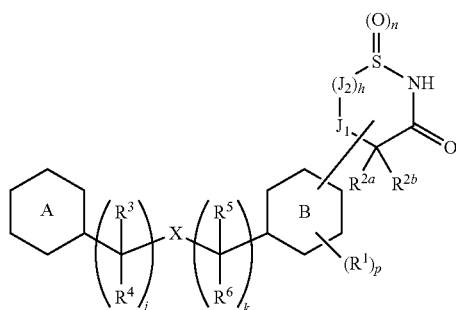
Particularly, among the compounds of the present invention, a compound having a 1-oxo-1,2-thiazolidin-3-one ring has such unexpected advantages as having a longer half-life in blood and having a reduced activity of inhibiting cytP-450 (CYP2C9) in comparison with a compound having an isothiazole-3-ol 1-oxide ring. In addition, it has been unexpectedly found that a compound having a 1,2-thiazinane-3-on 1,1-dioxide ring has a higher kinetic solubility and exhibits a more attenuated activity of inhibiting cytP-450 (CYP2C9) in comparison with a compound having an isothiazole-3-ol 1-oxide ring.

MODES FOR CARRYING OUT THE INVENTION

The present invention provides: a compound of Formula (I), characterized by having the cyclic amide structure shown in the following aspects, a salt of the compound, or a solvate of the compound or the salt; and a pharmaceutical composition or GPR40 activating agent, characterized by containing the compound, the salt, or the solvate as an active ingredient.

7

[Aspects of the Present Invention]
 [1] Aspect [1] of the present invention
 A first aspect of the present invention is
 a compound of Formula (I):



(where n is an integer of 0 to 2; p is an integer of 0 to 4; h is an integer of 0 to 3; j is an integer of 0 to 3; k is an integer of 0 to 2;

a ring A is a C₆₋₁₄ aryl group which is optionally substituted with 1 to 5 L(s), a 3- to 14-membered heterocyclic group which is optionally substituted with 1 to 5 L(s), a C₅₋₇ cycloalkyl group which is optionally substituted with 1 to 5 L(s), a C₅₋₇ cycloalkenyl group which is optionally substituted with 1 to 5 L(s), a 6- to 14-membered spiro ring group which is optionally substituted with 1 to 5 L(s), or a 2-phenylamino-2-oxoacetyl group which is optionally substituted with 1 to 5 L(s);

a ring B is a C₆₋₁₄ aryl group or a 5- to 14-membered heteroaryl group;

X is an oxygen atom, a sulfur atom, or —NR⁷—;

J₁ is —CR^{11a}R^{11b}— or —NR^{11c}—; J₂ is —CR^{12a}R^{12b}— or —NR^{12c}— (with the proviso that when J₁ is —NR^{11c}—, h is 0);

R¹s are independently a group optionally selected from a halogen atom, a C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₆ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, and a cyano group;

R^{2a} and R^{2b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, and a cyano group;

R³, R⁴, R⁵, R⁶, and R⁷ are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, and a C₂₋₆ alkynyl group;

R^{11a} and R^{11b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, a halogenated C₁₋₆ alkoxy group, a C₂₋₇ alkanoyl group, and a carboxy group which is optionally protected;

R^{12a} and R^{12b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, a halogenated C₁₋₆ alkoxy group, and a cyano group;

R^{11c} and R^{12c} are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, and a haloge-

8

nated C₁₋₆ alkyl group; with the proviso that in the cyclic amide structure moiety, there is not one of the substituents (R^{2b}, R^{11b}, R^{11c}, R^{12b}, or R^{12c}) on an atom to which the ring B is bonded;

5 Ls are independently a group optionally selected from a halogen atom, —OH, an oxo group, a cyano group, a C₁₋₁₀ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₁₀ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, —SH, —SF₅, a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^bR^c group, and a substituted spiro piperidylmethyl group;

R^a is a C₁₋₆ alkyl group or a halogenated C₁₋₆ alkyl group; R^b and R^c are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₂₋₇ alkanoyl group (the alkanoyl group is optionally substituted with —OH or a C₁₋₆ alkoxy group), a C₁₋₆ alkyl-sulfonyl group, an arylcarbonyl group, and a heterocyclic carbonyl group, where R^b and R^c optionally form together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI) or with a carbonyl group, and the cyclic group is optionally further substituted with 1 to 5 substituent(s) RII;

50 where the substituents RII may be the same as or different from each other and be each a group optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s));

65 the substituents RII may be the same as or different from each other and be each a group optionally selected from the substituents RI, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is

optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group;

R^d and R^e are independently a hydrogen atom or a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s));

R^{e1} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s));

R^{b1} and R^{c1} are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a C₂₋₇ alkanoyl group, and a C₁₋₆ alkylsulfonyl group, where R^{b1} and R^{c1} optionally form together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C₁₋₆ alkyl group) or with a carbonyl group (with the proviso that there are excluded a compound which is 5-[4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one; a compound in which a saturated cyclic amide structure having —S(O)_n—NH—CO— is 1,1-dioxo-1,2-thiazolidin-3-one, the ring B is a benzene ring, the ring B is bonded to J₁, k is 1, and in the ring B, a linker moiety containing X and the cyclic amide structure are positioned at a p-position; and a compound in which the cyclic amide structure is 1,1-dioxo-1,2,5-thiadiazolidin-3-one, the ring B is bonded to J_p, and in the ring B, the cyclic amide structure is bonded to an atom adjacent to an atom to which a linker containing X is bonded)), or

a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable solvate of the compound, or a pharmaceutically acceptable solvate of the salt.

Each group in Formula (I) according to Aspect [1] is specifically described below.

In the explanation of the compound according to the present invention, for example, “C₁₋₆” indicates that the number of constituent carbon atoms, which is the number of carbon atoms in a linear, branched, or cyclic group unless otherwise indicated, is 1 to 6. The number of constituent carbon atoms includes the total number of carbon atoms in a group having a linear or branched group substituted with a cyclic group or a cyclic group substituted with a linear or branched group. Therefore, as for an acyclic group, “C₁₋₆” means a “linear or branched chain with the number of constituent carbon atoms of 1 to 6”. As for a cyclic group, “C₁₋₆” means a “cyclic group with the number of ring-constituting carbon atoms of 1 to 6”. As for a group having an acyclic group and a cyclic group, “C₁₋₆” means a “group with the total number of carbon atoms of 1 to 6”.

The “alkyl group” is a linear, branched, or cyclic alkyl group. For example, examples of the “C₁₋₆ alkyl group” include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, and 2-methylcyclopropyl. Examples of the “C₁₋₁₀ alkyl group” include, in addition to the groups mentioned as the “C₁₋₆ alkyl group”, heptyl, 1-methylhexyl, octyl, 2-ethylhexyl, 1,1-dimethylhexyl, nonyl, decyl, cycloheptyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-methylcyclohexyl, 4,4-dimethylcyclohexyl, and 3,3,5,5-tetramethylcyclohexyl. The cyclic alkyl group is also expressed as “cycloalkyl group”. Examples of the “C₅₋₇ cycloalkyl group” include cyclopentyl, cyclohexyl, and cycloheptyl.

The “alkenyl group” is a linear, branched, or cyclic alkenyl group. For example, examples of the “C₂₋₆ alkenyl group” include vinyl, allyl, isopropenyl, 2-methylallyl, butenyl, pentenyl, isopentenyl, hexenyl, 1-cyclopropen-1-yl, 2-cyclopropen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 1-cyclohexen-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclopentadien-1-yl, and 2,5-cyclohexadien-1-yl. Examples of the “C₂₋₁₀ alkenyl group” include, in addition to the groups mentioned as the “C₂₋₆ alkenyl group”, heptenyl, octenyl, nonenyl, decenyl, 1-cyclohepten-1-yl, 1-cyclohexen-1-ylmethyl, 4-methyl-1-cyclohexen-1-yl, 4,4-dimethyl-1-cyclohexen-1-yl, and 3,3,5,5-tetramethyl-1-cyclohexen-1-yl. The cyclic alkenyl group is also expressed as “cycloalkenyl group”. Examples of the “C₅₋₇ cycloalkenyl group” include 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 1-cyclohexen-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, and 1-cyclohepten-1-yl.

The “alkynyl group” is a linear, branched, or cyclic alkynyl group. For example, examples of the “C₂₋₆ alkynyl group” include ethynyl, 1-propynyl, 2-propynyl, butynyl, pentynyl, and hexynyl. Examples of the “C₂₋₁₀ alkynyl group” include, in addition to the groups mentioned as the “C₂₋₆ alkynyl group”, heptynyl, octynyl, nonynyl, and decynyl.

The “alkoxy group” is a linear, branched, or cyclic alkoxy group and comprehensively a group of RO— (as for the C₁₋₆ alkoxy group, R is the C₁₋₆ alkyl group listed above). For example, examples of the “C₁₋₆ alkoxy group” include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, isohexyloxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 2,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,3-dimethylbutoxy, 3,3-dimethylbutoxy, 1-ethylbutoxy, 2-ethylbutoxy, 1,1,2-trimethylpropyloxy, 1,2,2-trimethylpropyloxy, 1-ethyl-1-methylpropyloxy, 1-ethyl-2-methylpropyloxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, 1-cyclopropylethoxy, 2-cyclopropylethoxy, 2-cyclobutylethoxy, and 2-methylcyclopropyloxy. Examples of the “C₁₋₁₀ alkoxy group” include, in addition to the groups mentioned as the “C₁₋₆ alkoxy group”, heptyloxy, octyloxy, 2-ethylhexyloxy, nonyloxy, decyloxy, cyclohepty-

11

loxy, cyclohexylmethoxy, 2-cyclohexylethoxy, 4-methylcyclohexyloxy, 4,4-dimethylcyclohexyloxy, and 3,3,5,5-tetramethylcyclohexyloxy.

The “alkenyloxy group” is the “alkenyl group” which is substituted with an oxygen atom, denoting a linear, branched, or cyclic alkenyloxy group. For example, examples of the “C₂₋₆ alkenyloxy group” include vinyloxy, allyloxy, isopropenyloxy, 2-methylallyloxy, butenyloxy, pentenyloxy, isopentenylloxy, hexenyloxy, 1-cyclopropen-1-yloxy, 2-cyclopropen-1-yloxy, 1-cyclobuten-1-yloxy, 1-cyclopenten-1-yloxy, 2-cyclopenten-1-yloxy, 3-cyclopenten-1-yloxy, 1-cyclohexen-1-yloxy, 2-cyclohexen-1-yloxy, 3-cyclohexen-1-yloxy, 2,4-cyclopentadien-1-yloxy, and 2,5-cyclohexadien-1-yloxy. Examples of the “C₂₋₁₀ alkenyloxy group” include, in addition to the groups mentioned as the “C₂₋₆ alkenyloxy group”, heptenyloxy, octenyloxy, nonenyloxy, decenyloxy, 1-cyclohepten-1-yloxy, 1-cyclohexen-1-yl-methoxy, 4-methyl-1-cyclohexen-1-yloxy, 4,4-dimethyl-1-cyclohexen-1-yloxy, and 3,3,5,5-tetramethyl-1-cyclohexen-1-yloxy.

The “alkynyloxy group” is the “alkynyl group” which is substituted with an oxygen atom, denoting a linear, branched, or cyclic alkynyloxy group. For example, examples of the “C₂₋₆ alkynyloxy group” include ethynyloxy, 1-propynyloxy, 2-propynyloxy, butynyloxy, pentynyloxy, and hexynyloxy. Examples of the “C₂₋₁₀ alkynyloxy group” include, in addition to the groups mentioned as the “C₂₋₆ alkynyloxy group”, heptynyloxy, octynyloxy, nonynyloxy, and decynyloxy.

Examples of the “aryl group” include a monocyclic or ring-fused C₆₋₁₄ aryl groups, for example, phenyl, 1-naphthyl, 2-naphthyl, anthryl, phenanthryl, and acenaphthyl, or a fused aryl group which is partly hydrogenated such as (1-, 2-, 4-, or 5-)indanyl, indenyl, and tetrahydronaphthyl. The fused aryl group which is partly hydrogenated means a monovalent group obtained by removing any hydrogen atom from a fused ring which is partly hydrogenated, and the hydrogen atom to be removed is optionally a hydrogen atom in an aromatic ring moiety or a hydrogen atom in a hydrogenated moiety of the fused ring. For example, tetrahydronaphthyl includes 1,2,3,4-tetrahydronaphthalene (-1-yl, -2-yl, -3-yl, -4-yl, -5-yl, -6-yl, -7-yl, -8-yl), and the like.

Examples of the “heterocyclic group” include a “heteroaryl group” and a saturated or unsaturated “non-aromatic heterocyclic group”. The term “cyclic” used for these groups means a monovalent group obtained by removing any hydrogen atom from a ring having a 3- to 14-membered, preferably a 3- to 12-membered, monocyclic ring or fused ring containing, in addition to carbon atoms, at least one (preferably 1 to 4) heteroatom(s) optionally selected from N, O, and S.

The “heteroaryl group” can be monocyclic or ring-fused, and the monocyclic heteroaryl group preferably has 5 to 7 ring members and examples of the “heteroaryl group” include pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2H-1,2,3-thiadiazinyl, 4H-1,2,4-thiadiazinyl, 6H-1,3,4-thiadiazinyl, 1,4-diazepinyl, and 1,4-oxazepinyl.

The ring-fused heteroaryl group preferably has 8 to 14 ring members and includes a monovalent group obtained by removing any hydrogen atom from a fused ring formed by fusing the 5- to 7-membered heterocyclic ring and a monocyclic aryl group or a monocyclic heteroaryl group, and the like. The hydrogen atom is optionally removed from any of the fused rings.

12

Specifically, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzimidazolyl, 1H-indazolyl, 1H-benzotriazolyl, 2,1,3-benzothiadiazinyl, chromenyl, isochromenyl, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, quinolyl, isoquinolyl, cinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, benzoxazepinyl, benzoazepinyl, benzodiazepinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, thieno[3,2-c]pyridyl, thiazolo[5,4-c]pyridyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,5-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, 1H-pyrazolo[3,4-b]pyridyl, 1,2,4-triazolo[1,5-a]pyrimidinyl, dibenzofuranyl, and the like are mentioned.

A ring-fused heteroaryl group, etc. which is partly hydrogenated, such as indolinyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, chromanyl, isochromanyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, tetrahydroquinoxalinyl, 1,3-benzodioxanyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, tetrahydrobenzoxazepinyl, tetrahydrobenzoazepinyl, and 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridyl is also mentioned. The ring-fused heteroaryl group, etc. which is partly hydrogenated is preferably one having 8 to 14 ring members, namely a monovalent group obtained by removing any hydrogen atom from a ring which is partly hydrogenated in the fused ring formed by fusing the 5- to 7-membered heterocyclic ring and a monocyclic aryl group or a monocyclic heteroaryl group. The hydrogen atom to be removed is optionally a hydrogen atom in the aryl group or in the heterocyclic moiety or a hydrogen atom in the hydrogenated moiety. In the case of tetrahydroquinolyl, examples of the partly hydrogenated ring-fused heteroaryl group include 5,6,7,8-tetrahydroquinolyl and 1,2,3,4-tetrahydroquinolyl. Depending on the position in these groups from which the hydrogen atom is removed, -2-yl, -3-yl, -4-yl, -5-yl, -6-yl, -7-yl, and -8-yl are exemplified in the case of 5,6,7,8-tetrahydroquinolyl, and in the case of 1,2,3,4-tetrahydroquinolyl, -1-yl, -2-yl, -3-yl, -4-yl, -5-yl, -6-yl, -7-yl, and -8-yl are exemplified.

Examples of the “non-aromatic heterocyclic group” include a 3- to 8-membered saturated or unsaturated non-aromatic heterocyclic group, for example, aziridinyl, azetidiny, oxiranyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, pyrazolinyl, pyrazolidinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl (oxanyl), tetrahydrothiopyranyl, piperazinyl, dioxanyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxadiazolinyl, oxadiazolidinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, and oxepanyl, and the “non-aromatic heterocyclic group” means a monovalent group obtained by removing any hydrogen atom from the ring.

Examples of the “heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s))” include, in addition to the groups mentioned as the “heterocyclic group”, a group in which the cyclic group is substituted with 1 to 3 “C₁₋₆ alkyl group(s)” or 1 to 3 oxo group(s) at any position. For example, methylpyrrolyl, methylfuryl, methylthienyl, methylimidazolyl, methylpyrazolyl, methylloxazolyl, methylisoxazolyl, methylthiazolyl, methylisothiazolyl, methylpyridyl, methylpyrimidinyl,

13

methylaziridinyl, methylazetidiny, methyloxiranyl, methyloxetanyl, methylthietanyl, methylpyrrolidinyl, methyltetrahydrofuryl, methylthiolanyl, methylpyrazolinyl, methylpyrazolidinyl, methylpiperidinyl, methyltetrahydropyranyl, methylpiperazinyl, methyloxazolonyl, methylisoxazolonyl, methyloxazolidinyl, methylisoxazolidinyl, methylthiazolinyl, methylisothiazolinyl, methylthiazolidinyl, methylisothiazolidinyl, methyloxadiazolinyl, methyloxadiazolidinyl, methylmorpholinyl, methylthiomorpholinyl, methylquinclidinyl, methylloxepanyl, oxopyrrolidinyl, 1,1-dioxidetetrahydrothiopyranyl, and the like are mentioned.

The “aralkyl group” is a group in which a linear or branched alkyl group of the “C₁₋₆ alkyl group” is substituted with the “aryl group”, and examples of the “aralkyl group” include benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, 1-indanylmethyl, 2-indanylmethyl, 1,2,3,4-tetrahydronaphthalen-1-ylmethyl, and 1,2,3,4-tetrahydronaphthalen-2-ylmethyl.

The “heteroarylalkyl group” is a group in which a linear or branched alkyl group of the “C₁₋₆ alkyl group” is substituted with the “heteroaryl group”, and examples of the “heteroarylalkyl group” include those substituted with the “monocyclic heteroaryl group”, such as pyrrolylmethyl, furylmethyl, thienylmethyl, imidazolylmethyl, pyrazolylmethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, 1,2,3-triazolylmethyl, 1,2,4-triazolylmethyl, 1,2,3-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,3,4-oxadiazolylmethyl, furazanylmethyl, 1,2,3-thiadiazolylmethyl, 1,2,4-thiadiazolylmethyl, 1,3,4-thiadiazolylmethyl, tetrazolylmethyl, pyridylmethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, 1,2,3-triazinylmethyl, 1,2,4-triazinylmethyl, 1,3,5-triazinylmethyl, 2H-1,2,3-thiadiazinylmethyl, 4H-1,2,4-thiadiazinylmethyl, 6H-1,3,4-thiadiazinylmethyl, 1,4-diazepinylmethyl, and 1,4-oxazepinylmethyl, and

those substituted with the “ring-fused heteroaryl group”, such as indolylmethyl, isoindolylmethyl, benzofuranylmethyl, isobenzofuranylmethyl, benzothienylmethyl, isobenzothienylmethyl, benzoxazolylmethyl, 1,2-benzisoxazolylmethyl, benzothiazolylmethyl, 1,2-benzisothiazolylmethyl, 1H-benzimidazolylmethyl, 1H-indazolylmethyl, 1H-benzotriazolylmethyl, 2,1,3-benzothiadiazinylmethyl, chromenylmethyl, isochromenylmethyl, 4H-1,4-benzoxazinylmethyl, 4H-1,4-benzothiazinylmethyl, quinolylmethyl, isoquinolylmethyl, cinnolylmethyl, quinazolinylmethyl, quinoxalinylmethyl, phthalazinylmethyl, benzoxazepinylmethyl, benzozazepinylmethyl, benzodiazepinylmethyl, naphthyridinylmethyl, purinylmethyl, pteridinylmethyl, carbazolylmethyl, carbolinylmethyl, acridinylmethyl, phenoxazinylmethyl, phenothiazinylmethyl, phenazinylmethyl, phenoxathiinylmethyl, thianthrenylmethyl, phenanthridinylmethyl, phenanthrolinylmethyl, indolizinylmethyl, thieno[3,2-c]pyridylmethyl, thiazolo[5,4-c]pyridylmethyl, pyrrolo[1,2-b]pyridazinylmethyl, pyrazolo[1,5-a]pyridylmethyl, imidazo[1,2-a]pyridylmethyl, imidazo[1,5-a]pyridylmethyl, imidazo[1,2-b]pyridazinylmethyl, imidazo[1,5-a]pyrimidinylmethyl, 1,2,4-triazolo[4,3-a]pyridylmethyl, 1,2,4-triazolo[4,3-b]pyridazinylmethyl, 1H-pyrazolo[3,4-b]pyridylmethyl, 1,2,4-triazolo[1,5-a]pyrimidinylmethyl, indolylmethyl, dihydrobenzofuranylmethyl, chromanylmethyl, tetrahydroquinolylmethyl, tetrahydroisoquinolylmethyl, 1,4-benzodioxanylmethyl, and 1,3-benzodioxolylmethyl.

The “non-aromatic heterocyclic alkyl group” is a group in which a linear or branched alkyl group of the “C₁₋₆ alkyl

14

group” is substituted with the “non-aromatic heterocyclic group”, and examples of the “non-aromatic heterocyclic alkyl group” include aziridinylmethyl, azetidinylmethyl, oxiranylmethyl, oxetanylmethyl, thietanylmethyl, pyrrolidinylmethyl, tetrahydrofurylmethyl, thiolanylmethyl, pyrazolinylmethyl, pyrazolidinylmethyl, piperidinylmethyl, dihydropyranylmethyl, tetrahydropyranylmethyl, tetrahydrothiopyranylmethyl, piperazinylmethyl, dioxanylmethyl, oxazolinylmethyl, isoxazolinylmethyl, oxazolidinylmethyl, isoxazolidinylmethyl, thiazolinylmethyl, isothiazolinylmethyl, thiazolidinylmethyl, isothiazolidinylmethyl, oxadiazolinylmethyl, oxadiazolidinylmethyl, morpholinylmethyl, thiomorpholinylmethyl, quinuclidinylmethyl, and oxepanylmethyl.

The “aryloxy group” is the “aryl group” which is substituted with an oxygen atom, and specifically, a group in which the group mentioned as the “aryl group” is substituted with an oxygen atom is mentioned. For example, examples of the “aryloxy group” include phenoxy, 1-naphthylloxy, 2-naphthylloxy, 2-anthryloxy, phenanthryloxy, 1-indanyloxy, 2-indanyloxy, 1,2,3,4-tetrahydronaphthalen-1-yloxy, 1,2,3,4-tetrahydronaphthalen-2-yloxy, and 1,2,3,4-tetrahydronaphthalen-8-yloxy.

The “heterocyclic oxy group” is the “heterocyclic group” which is substituted with an oxygen atom, and a “heteroaryloxy group” or a “non-aromatic heterocyclic oxy group” is mentioned. Specifically, a group in which the group mentioned as the “heterocyclic group” is substituted with an oxygen atom is mentioned.

The “heteroaryloxy group” is the “heteroaryl group” which is substituted with an oxygen atom, and specifically, a group in which the group mentioned as the “heteroaryl group” is substituted with an oxygen atom is mentioned. For example, examples of the “heteroaryloxy group” include pyrrolyloxy, furyloxy, thienyloxy, imidazolyloxy, pyrazolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, (2-, 3-, or 4-)pyridyloxy, pyridazinolyloxy, pyrimidinolyloxy, pyrazinyloxy, indolyloxy, quinolyloxy, isoquinolyloxy, indolinyloxy, dihydrobenzofuranyloxy, chromanyloxy, tetrahydroquinolyloxy, tetrahydroisoquinolyloxy, 1,4-benzodioxanyloxy, and 1,3-benzodioxolyloxy.

The “non-aromatic heterocyclic oxy group” is the “non-aromatic heterocyclic group” which is substituted with an oxygen atom, and specifically, a group in which the group mentioned as the “non-aromatic heterocyclic group” is substituted with an oxygen atom is mentioned. Examples of the “non-aromatic heterocyclic oxy group” include 3- to 8-membered saturated or unsaturated non-aromatic heterocyclic oxy groups such as aziridinolyloxy, azetidinyloxy, oxiranyloxy, oxetanyloxy, thietanyloxy, pyrrolidinolyloxy, tetrahydrofuryloxy, thiolanyloxy, pyrazolinolyloxy, pyrazolidinyloxy, (1-, 2-, 3-, or 4-)piperidinolyloxy, dihydropyranyloxy, (2-, 3-, or 4-)tetrahydropyranyloxy ((2-, 3-, or 4-)oxanyloxy), tetrahydrothiopyranyloxy, piperazinolyloxy, dioxanyloxy, oxazolinyloxy, isoxazolinyloxy, oxazolidinyloxy, isoxazolidinyloxy, thiazolinyloxy, isothiazolinyloxy, thiazolidinyloxy, isothiazolidinyloxy, oxadiazolinyloxy, oxadiazolidinyloxy, morpholinolyloxy, thiomorpholinolyloxy, quinuclidinyloxy, and oxepanyloxy.

Examples of the “heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s))” include, in addition to the groups mentioned as the “heterocyclic oxy group”, a group in which the cyclic group is substituted with 1 to 3 “C₁₋₆ alkyl group(s)” or 1 to 3 oxo group(s) at any position. The “heterocyclic oxy group” can also be expressed as a group in which the “heterocyclic group (the heterocyclic group is optionally

15

substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s))” is substituted with an oxygen atom, and specifically, a group in which the groups mentioned as the “heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s))” are substituted with an oxygen atom, is mentioned.

The “aralkyloxy group” is the “aralkyl group” which is substituted with an oxygen atom, and specifically, a group in which the groups mentioned as the “aralkyl group” are substituted with an oxygen atom is mentioned. For example, examples of the “aralkyloxy group” include benzyloxy, phenethyloxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-naphthylmethoxy, 2-(1-naphthyl)ethoxy, 2-(2-naphthyl)ethoxy, 1-indanylmethoxy, 2-indanylmethoxy, 1,2,3,4-tetrahydronaphthalene-1-ylmethoxy, and 1,2,3,4-tetrahydronaphthalene-2-ylmethoxy.

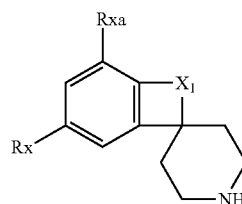
The “heteroarylalkyloxy group” is the “heteroarylalkyl group” which is substituted with an oxygen atom, and specifically, a group in which the groups mentioned as the “heteroarylalkyl group” are substituted with an oxygen atom is mentioned. For example, a “monocyclic heteroarylalkyl group” substituted with an oxygen atom, such as pyrrolylmethoxy, furylmethoxy, thienylmethoxy, imidazolylmethoxy, pyrazolylmethoxy, oxazolylmethoxy, isoxazolylmethoxy, thiazolylmethoxy, isothiazolylmethoxy, 1,2,3-triazolylmethoxy, 1,2,4-triazolylmethoxy, 1,2,3-oxadiazolylmethoxy, 1,2,4-oxadiazolylmethoxy, 1,3,4-oxadiazolylmethoxy, furazanylmethoxy, 1,2,3-thiadiazolylmethoxy, 1,2,4-thiadiazolylmethoxy, 1,3,4-thiadiazolylmethoxy, tetrazolylmethoxy, pyridylmethoxy, pyridazinylmethoxy, pyrimidinylmethoxy, pyrazinylmethoxy, 1,2,3-triazinylmethoxy, 1,2,4-triazinylmethoxy, 1,3,5-triazinylmethoxy, 2H-1,2,3-thiadiazinylmethoxy, 4H-1,2,4-thiadiazinylmethoxy, 6H-1,3,4-thiadiazinylmethoxy, 1,4-diazepinylmethoxy, 1,4-oxazepinylmethoxy, and the like, and

a “ring-fused heteroarylalkyl group” which is optionally partly hydrogenated and is substituted with an oxygen atom, such as indolylmethoxy, isoindolylmethoxy, benzofuranyl methoxy, isobenzofuranyl methoxy, benzothienylmethoxy, isobenzothienylmethoxy, benzoxazolylmethoxy, 1,2-benzisoxazolylmethoxy, benzothiazolylmethoxy, 1,2-benzisothiazolylmethoxy, 1H-benzimidazolylmethoxy, 1H-indazolylmethoxy, 1H-benzotriazolylmethoxy, 2,1,3-benzothiadiazinylmethoxy, chromenylmethoxy, isochromenylmethoxy, 4H-1,4-benzoxazinylmethoxy, 4H-1,4-benzothiazinylmethoxy, quinolylmethoxy, isoquinolylmethoxy, cinnolylmethoxy, quinazolinylmethoxy, quinoxalinylmethoxy, phthalazinylmethoxy, benzoxazepinylmethoxy, benzoazepinylmethoxy, benzodiazepinylmethoxy, naphthyridinylmethoxy, purinylmethoxy, pteridinylmethoxy, carbazolylmethoxy, carbolinylmethoxy, acridinylmethoxy, phenoxazinylmethoxy, phenothiazinylmethoxy, phenazinylmethoxy, phenoxathiinylmethoxy, thianthrenylmethoxy, phenanthridinylmethoxy, phenanthrolinylmethoxy, indolizinylnmethoxy, thieno[3,2-c]pyridylmethoxy, thiazolo[5,4-c]pyridylmethoxy, pyrrolo[1,2-b]pyridazinylmethoxy, pyrazolo[1,5-a]pyridylmethoxy, imidazo[1,2-a]pyridylmethoxy, imidazo[1,5-a]pyridylmethoxy, imidazo[1,2-b]pyridazinylmethoxy, imidazo[1,5-a]pyrimidinylmethoxy, 1,2,4-triazolo[4,3-a]pyridylmethoxy, 1,2,4-triazolo[4,3-b]pyridazinylmethoxy, 1H-pyrazolo[3,4-b]pyridylmethoxy, 1,2,4-triazolo[1,5-a]pyrimidinylmethoxy, indolinylnmethoxy, dihydrobenzofuranyl methoxy, chromanyl methoxy, tetrahydroquinolylmethoxy, tetrahydroisoquinolylmethoxy, 1,4-benzodioxanyl methoxy, 1,3-benzodioxolylmethoxy, and the like, are mentioned.

16

The “spiro ring group” is a 6- to 18-membered mono spirocyclic group in which two cyclic groups share one atom as a spiro atom to be spiro-fused. Each cyclic group forming a spiro ring is a carbon ring group (such as a cyclic alkyl group and a partly hydrogenated fused aryl group) or a heterocyclic group (such as a non-aromatic heterocyclic group and a partly hydrogenated ring-fused heteroaryl group) and may be a monocyclic ring or a fused ring. The number of members of the spiro ring group is preferably 6 to 14, and when each cyclic group forming the spiro ring is monocyclic, the cyclic groups are independently preferably a 3- to 7-membered cyclic group. Each cyclic group forming the spiro ring may independently have, in the ring, 1 to 3 double bond(s), preferably 1 double bond. Examples of the “spiro ring group” include spiro[4,4]nona-(1- or 2-)ene-2-yl, spiro[4,5]dec-(1- or 2-)ene-2-yl, spiro[4,5]dec-(6- or 7-)ene-7-yl, spiro[5,5]undec-2-yl, spiro[5,5]undec-(1- or 2-)ene-2-yl, spiro[inden-1,4'-piperidin]-1'-yl, spiro[indolin-3,4'-piperidin]-1'-yl, and spiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl. These spiro rings are optionally substituted with, for example, 1 to 5 halogen atom(s), 1 to 5 —OH group(s), 1 to 5 C₁₋₆ alkyl group(s), 1 to 5 halogenated C₁₋₆ alkyl group(s), 1 to 5 C₁₋₆ alkoxy group(s), or 1 to 5 oxo group(s) which may be the same as or different from each other.

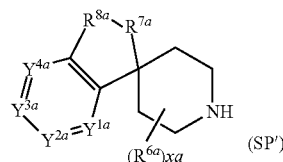
The “substituted spiropiperidinylmethyl group” is a methyl group to which a substituted spiropiperidinyl group defined by Formula (SP):



(SP)

(where Rx and Rxa are independently a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, a C₁₋₃ alkyl group, a trifluoromethyl group, and a methoxy group; X₁ is —CH(Ry)CH₂—, —C(Ry)=CH—, —N(Rz)CH₂—, or —C(O)CH₂—;

Ry is a hydrogen atom or a C₁₋₃ alkyl group; and Rz is a hydrogen atom, a C₁₋₃ alkyl group, or a phenyl group) is bonded, or a methyl group to which Formula (SP'):



(SP')

(where R^{6a}s are independently a halogen atom or a C₁₋₃ alkyl group; xa is an integer of 0 to 8; R^{7a} is an oxygen atom or —CH₂—, R^{8a} is an oxygen atom, —CH₂—, or —C(O)—, or R^{7a} and R^{8a} together optionally form —CH=CH— (with the proviso that R^{7a} and R^{8a} are not simultaneously an oxygen atom); Y^{1a} is —CR^{9a}— or a nitrogen atom, Y^{2a} is —CR^{9b}— or a nitrogen atom, Y^{3a} is —CR^{9c}— or a nitrogen atom, and Y^{4a} is —CR^{9d}— or a nitrogen atom; and R^{9a}, R^{9b}, R^{9c}, and R^{9d} are independently a hydrogen atom, a halogen atom, or a

Examples of the “halogen atom” include a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

The “halogenated C₁₋₆ alkyl group” is a group in which the “C₁₋₆ alkyl group” is optionally substituted with 1 to 5 halogen atom(s). For example, trifluoromethyl, trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, and the like are mentioned.

The “halogenated C₁₋₆ alkoxy” is a group in which the “C₁₋₆ alkoxy” is optionally substituted with 1 to 5 halogen atom(s). For example, trifluoromethoxy, trifluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and the like are mentioned.

Examples of the protective group for the “carboxy which is optionally protected” include: an alkyl ester-based protective group such as methyl, ethyl, tert-butyl, benzyl, diphenylmethyl, and trityl; and a silyl ester-based protective group such as trimethylsilyl and tert-butyldimethylsilyl.

The “C₂₋₇ alkanoyl group” means a “linear, branched, or cyclic C₂₋₇ alkylcarbonyl group” and is expressed as R—CO— (R is the “C₁₋₆ alkyl group”). Examples thereof include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cyclopropylmethylcarbonyl, and 2-methylcyclopropylcarbonyl.

Examples of the “C₂₋₇ alkanoyl group (the alkanoyl group is optionally substituted with —OH or a C₁₋₆ alkoxy group)” include, in addition to the groups mentioned as the “C₂₋₇ alkanoyl group”, a group in which the alkanoyl group is substituted with —OH or a C₁₋₆ alkoxy group at any position and specific examples thereof include hydroxyacetyl and methoxyacetyl.

The “arylcarbonyl group” is a group in which a carbonyl group is bonded to the “aryl group”, and examples thereof include C₆₋₁₄ arylcarbonyl such as benzoyl and naphthylcarbonyl.

The “heterocyclic carbonyl group” means a “heterocyclic carbonyl group”, and examples thereof include the “heterocyclic group” (for example, a heteroaryl group, a saturated or unsaturated non-aromatic heterocyclic group, and the like) to which a carbonyl group is bonded, including a carbonyl group to which the “monocyclic heteroaryl group” is bonded, such as pyrrolylcarbonyl, furylcarbonyl, thienylcarbonyl, imidazolylcarbonyl, pyrazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, isothiazolylcarbonyl, 1,2,3-triazolylcarbonyl, 1,2,4-triazolylcarbonyl, 1,2,3-oxadiazolylcarbonyl, 1,2,4-oxadiazolylcarbonyl, 1,3,4-oxadiazolylcarbonyl, furazanylcarbonyl, 1,2,3-thiadiazolylcarbonyl, 1,2,4-thiadiazolylcarbonyl, 1,3,4-thiadiazolylcarbonyl, tetrazolylcarbonyl, pyridylcarbonyl, pyridazinylcarbonyl, pyrimidinylcarbonyl, pyrazinylcarbonyl, 1,2,3-triazinylcarbonyl, 1,2,4-triazinylcarbonyl, 1,3,5-triazinylcarbonyl, 2H-1,2,3-thiadiazinylcarbonyl, 4H-1,2,4-thiadiazinylcarbonyl, 6H-1,3,4-thiadiazinylcarbonyl, 1,4-diazepinylcarbonyl, and 1,4-oxazepinylcarbonyl; a carbonyl group to which the “ring-fused heteroaryl group” which is optionally partly hydrogenated is bonded, such as indolylcarbonyl, isoindolylcarbonyl, benzofuranylcarbonyl, isobenzofuranylcarbonyl, benzothienylcarbonyl, isobenzothienylcarbonyl, benzoxazolylcarbonyl, 1,2-benzisoxazolylcarbonyl, benzothiazolylcarbonyl, 1,2-benzisothiazolylcarbonyl, 1H-benzimidazolylcarbonyl, 1H-indazolylcarbonyl, 1H-benzotriazolylcarbonyl, 2,1,3-benzothiadiazinylcarbonyl, chromenylcarbonyl, isochromenylcarbonyl, 4H-1,4-benzoxazinylcarbonyl, 4H-1,4-benzothiazinylcarbonyl, quinolylcarbonyl, isoquinolylcarbonyl, cinnolylcarbonyl, quinoxalinylcarbonyl, quinoxalinylcarbonyl, phthalazinylcarbonyl, benzoxazepinylcarbonyl, benzoazepinylcarbonyl, benzodiazepinylcarbonyl, naphthyridinylcarbonyl, purinylcarbonyl, pteridinylcarbonyl, carbazolylcarbonyl, carboli-

nylcarbonyl, acridinylcarbonyl, phenoxazinylcarbonyl, phenothiazinylcarbonyl, phenazinylcarbonyl, phenoxathiinylcarbonyl, thianthrenylcarbonyl, phenanthridinylcarbonyl, phenanthrolinylcarbonyl, indolizinyllcarbonyl, thieno[3,2-c]pyridylcarbonyl, thiazolo[5,4-c]pyridylcarbonyl, pyrrolo[1,2-b]pyridazinylcarbonyl, pyrazolo[1,5-a]pyridylcarbonyl, imidazo[1,2-a]pyridylcarbonyl, imidazo[1,5-a]pyridylcarbonyl, imidazo[1,2-b]pyridazinylcarbonyl, imidazo[1,5-a]pyrimidinylcarbonyl, 1,2,4-triazolo[4,3-a]pyridylcarbonyl, 1,2,4-triazolo[4,3-b]pyridazinylcarbonyl, 1H-pyrazolo[3,4-b]pyridylcarbonyl, 1,2,4-triazolo[1,5-a]pyrimidinylcarbonyl, indolinylcarbonyl, dihydrobenzofuranylcarbonyl, chromanylcarbonyl, tetrahydroquinolylcarbonyl, tetrahydroisoquinolylcarbonyl, 1,4-benzodioxanylcarbonyl, and 1,3-benzodioxolylcarbonyl, and

a carbonyl group to which the “saturated or unsaturated non-aromatic heterocyclic group” is bonded, such as aziridinylcarbonyl, azetidinyllcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, piperidinylcarbonyl, tetrahydropyranylcarbonyl, piperazinylcarbonyl, and morpholinylcarbonyl.

The “non-aromatic heterocyclic carbonyl group” is the “heterocyclic carbonyl group” in which the “heterocyclic group” is a “non-aromatic heterocyclic group”, that is, a group in which a carbonyl group is bonded to the “non-aromatic heterocyclic group”. Specifically, a carbonyl group to which the “saturated or unsaturated non-aromatic heterocyclic group” mentioned as the “heterocyclic carbonyl group” is bonded is mentioned.

In the “—COOR^f group”, R^f is a hydrogen atom or a C₁₋₆ alkyl group and means a carboxy group or an alkoxycarbonyl group. Specifically, for example, carboxy, methoxycarbonyl, ethoxycarbonyl, and the like are mentioned.

In the “—S(O)_iR^a group”, i is an integer of 0 to 2, and R^a is a group optionally selected from a C₁₋₆ alkyl group and a halogenated C₁₋₆ alkyl group. When i is 0, examples of the “—S(O)_iR^a group” include a “C₁₋₆ alkylthio group” and a “halogenated C₁₋₆ alkylthio group”, when i is 1, examples of the “—S(O)_iR^a group” include a “C₁₋₆ alkylsulfinyl group” and a “halogenated C₁₋₆ alkylsulfinyl group”, and when i is 2, examples of the “—S(O)_iR^a group” include a “C₁₋₆ alkylsulfonyl group” and a “halogenated C₁₋₆ alkylsulfonyl group”.

The “C₁₋₆ alkylthio group” means a linear, branched, or cyclic C₁₋₆ alkylthio group, and examples thereof include methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, tert-pentylthio, 1-methylbutylthio, 2-methylbutylthio, 1,2-dimethylpropylthio, 1-ethylpropylthio, hexylthio, isohexylthio, 1-methylpentylthio, 2-methylpentylthio, 3-methylpentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 2,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1,2-trimethylpropylthio, 1,2,2-trimethylpropylthio, 1-ethyl-1-methylpropylthio, 1-ethyl-2-methylpropylthio, cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cyclopropylmethylthio, cyclobutylmethylthio, cyclopentylmethylthio, 1-cyclopropylethylthio, 2-cyclopropylethylthio, 2-cyclobutylethylthio, and 2-methylcyclopropylthio. The “halogenated C₁₋₆ alkylthio group” is a group in which the “C₁₋₆ alkylthio group” is optionally substituted with 1 to 5 halogen atom(s), and examples thereof include trifluoromethylthio.

The “C₁₋₆ alkylsulfinyl group” means a linear, branched, or cyclic C₁₋₆ alkylsulfinyl group, and examples thereof include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, cyclopropylsulfinyl, cyclopropylmethylsulfinyl, and 2-methylcyclopropylsulfinyl. The “halogenated C₁₋₆ alkyl-

21

sulfinyl group" is a group in which the "C₁₋₆ alkylsulfinyl group" is optionally substituted with 1 to 5 halogen atom(s), and examples thereof include trifluoromethylsulfinyl.

The "C₁₋₆ alkylsulfonyl group" means a linear, branched, or cyclic C₁₋₆ alkylsulfonyl group, and examples thereof include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, cyclopropylsulfonyl, cyclopropylmethylsulfonyl, and 2-methylcyclopropylsulfonyl. The "halogenated C₁₋₆ alkylsulfonyl group" is a group in which the "C₁₋₆ alkylsulfonyl group" is optionally substituted with 1 to 5 halogen atom(s), and examples thereof include trifluoromethylsulfonyl.

The "—SO₂NR^dR^e group", in which R^d and R^e are independently a hydrogen atom or a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)), means, in addition to a sulfamoyl group in which 1 or 2 hydrogen atom(s) on a nitrogen atom of the sulfamoyl group is(are) optionally substituted with the "C₁₋₆ alkyl group", a sulfamoyl group substituted with a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)). Specifically, for example, a sulfamoyl group, a methylsulfamoyl group, an ethylsulfamoyl group, a propylsulfamoyl group, an isopropylsulfamoyl group, a cyclopropylsulfamoyl group, a butylsulfamoyl group, an isobutylsulfamoyl group, a pentylsulfamoyl group, an isopentylsulfamoyl group, a hexylsulfamoyl group, an isohexylsulfamoyl group, a dimethylsulfamoyl group, a diethylsulfamoyl group, a dipropylsulfamoyl group, a di-isopropylsulfamoyl group, a dibutylsulfamoyl group, a dipentylsulfamoyl group, an ethylmethylsulfamoyl group, a methylpropylsulfamoyl group, an ethylpropylsulfamoyl group, a butylmethylsulfamoyl group, a butylethylsulfamoyl group, a butylpropylsulfamoyl group, a trifluoromethylsulfamoyl group, a hydroxymethylsulfamoyl group, a 2-hydroxyethylsulfamoyl group, a 3-hydroxypropylsulfamoyl group, a 3-hydroxybutylsulfamoyl group, a 2,3-dihydroxypropylsulfamoyl group, a 3-hydroxy-2-hydroxymethylpropylsulfamoyl group, a 3-hydroxy-2-hydroxymethyl-2-methylpropylsulfamoyl group, a 2-methoxyethylsulfamoyl group, a 2-ethoxyethylsulfamoyl group, a 2-methoxy-3-hydroxypropylsulfamoyl group, and the like are mentioned.

The "—CONR^dR^e group", in which R^d and R^e are independently a hydrogen atom or a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)), means, in addition to a carbamoyl group in which 1 or 2 hydrogen atom(s) on a nitrogen atom of the carbamoyl group is(are) optionally substituted with the "C₁₋₆ alkyl group", a carbamoyl group substituted with a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)). Specifically, for example, a carbamoyl group, a methylcarbamoyl group, an ethylcarbamoyl group, a propylcarbamoyl group, an isopropylcarbamoyl group, a cyclopropylcarbamoyl group, a butylcarbamoyl group, an isobutylcarbamoyl group, a pentylcarbamoyl group, an isopentylcarbamoyl group, a hexylcarbamoyl group, an isohexylcarbamoyl group, a dimethylcarbamoyl group, a diethylcarbamoyl group, a dipropylcarbamoyl group, a di-isopropylcarbamoyl group, a dibutylcarbamoyl group, a dipentylcarbamoyl group, an ethylmethylcarbamoyl group, a methylpropylcarbamoyl group, an ethylpropylcarbamoyl group, a butylmethylcarbamoyl group, a butylethylcarbamoyl group, a butylpropylcarbamoyl group, a trifluoromethylcarbamoyl group, a hydroxymethylcarbamoyl group, a 2-hydroxyethylcarbamoyl group, a 3-hydroxypropylcarbamoyl group, a 3-hydroxybutylcarbamoyl group, a 2,3-dihydroxypropylcarbamoyl group, a 3-hydroxy-2-hydroxymethylpropylcarbamoyl group, a 3-hydroxy-2-hydroxymethyl-2-methylpropylcarbamoyl group, a 2-methoxyethylcarbamoyl group, a 2-ethoxyethylcarbamoyl group, a 2-methoxy-3-hydroxypropylcarbamoyl group, and the like are mentioned.

22

oyl group, a 3-hydroxypropylcarbamoyl group, a 3-hydroxybutylcarbamoyl group, a 3-hydroxy-3-methylbutylcarbamoyl group, a 2,3-dihydroxypropylcarbamoyl group, a 3-hydroxy-2-hydroxymethylpropylcarbamoyl group, a 3-hydroxy-2-hydroxymethyl-2-methylpropylcarbamoyl group, a 2-methoxyethylcarbamoyl group, a 2-ethoxyethylcarbamoyl group, a 2-methoxy-3-hydroxypropylcarbamoyl group, and the like are mentioned.

In the "—CONR^dR^{e1} group", R^d is a hydrogen atom or a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)), and R^{e1} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a group(s) (i is an integer of 0 to 2), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^bR^{c1} group(s)). That is to say, the "—CONR^dR^{e1} group" means, in addition to a carbamoyl group in which one hydrogen atom on a nitrogen atom of the carbamoyl group is substituted with R^{e1}, a carbamoyl group in which another hydrogen atom on the nitrogen atom of the carbamoyl group is substituted with a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₆ alkoxy group(s)). Specifically, for example, a hydroxymethylcarbamoyl group, a 2-hydroxyethylcarbamoyl group, a 3-hydroxypropylcarbamoyl group, a 3-hydroxybutylcarbamoyl group, a 3-hydroxy-3-methylbutylcarbamoyl group, a 2,3-dihydroxypropylcarbamoyl group, a 3-hydroxy-2-hydroxymethylpropylcarbamoyl group, a 3-hydroxy-2-hydroxymethyl-2-methylpropylcarbamoyl group, a 2-methoxyethylcarbamoyl group, a 2-ethoxyethylcarbamoyl group, a 2-methoxy-3-hydroxypropylcarbamoyl group, a 3-methylsulfonyl-propylcarbamoyl group, a 2-(morpholin-4-yl)ethylcarbamoyl group, a 2-(4-methylpiperazin-1-yl)ethylcarbamoyl group, a 2-(2-oxopyrrolidin-1-yl)ethylcarbamoyl group, a 3-(2-oxopyrrolidin-1-yl)propylcarbamoyl group, a (5-oxopyrrolidin-2-yl)methylcarbamoyl group, a 3-(2-oxooxazolidin-3-yl)propylcarbamoyl group, a (3-methylxetan-3-yl)methylcarbamoyl group, a 3-(methylsulfonylamino)propylcarbamoyl group, and the like are mentioned.

In the "—NR^bR^c group", R^b and R^c are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₂₋₇ alkanoyl group (the alkanoyl group is optionally substituted with —OH or a C₁₋₆ alkoxy group), a C₁₋₆ alkylsulfonyl group, an arylcarbonyl group, and a heterocyclic carbonyl group. R^b and R^c optionally form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI) or with a carbonyl group, and the cyclic group is optionally further substituted with 1 to 5 substituent(s) RII. Examples of the "—NR^bR^c group" include amino, "mono/di C₁₋₆ alkylamino", "halogenated mono/di C₁₋₆ alkylamino", "mono/di C₂₋₆ alkenylamino", "mono/di C₂₋₆ alkynylamino", "C₂₋₇ alkanoylamino which is optionally substituted with —OH or C₁₋₆ alkoxy", "C₁₋₆ alkylsulfonylamino", "arylcarbonylamino", and "heterocyclic carbonylamino".

In the "—NR^{b1}R^{c1} group", R^{b1} and R^{c1} are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a C₂₋₇ alkanoyl group, and a C₁₋₆ alkylsulfonyl

group. R^{b1} and R^{c1} optionally form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one carbon atom is optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C_{1-6} alkyl group) or with a carbonyl group. Examples of the “ $—NR^{b1}R^{c1}$ group” include amino, “mono/di C_{1-6} alkylamino”, “ C_{2-7} alkanoylamino”, and “ C_{1-6} alkylsulfonylamino”.

The “mono/di C_{1-6} alkylamino” means an amino group, 1 or 2 hydrogen atom(s) of which is(are) substituted with a linear, branched, or cyclic “ C_{1-6} alkyl group”. Specifically, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, pentylamino, isopentylamino, hexylamino, isohexylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, 1-cyclopropylmethylamino, 1-cyclobutylmethylamino, 1-cyclopentylmethylamino, 1-cyclohexylmethylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, dipentylamino, ethylmethylamino, propylmethylamino, propylethylamino, butylmethylamino, butylethylamino, butylpropylamino, N-cyclopropyl-N-methylamino, N-cyclobutyl-N-methylamino, N-cyclopentyl-N-methylamino, N-cyclohexyl-N-methylamino, and the like are mentioned.

The “halogenated mono/di C_{1-6} alkylamino” is a group in which the “mono/di C_{1-6} alkylamino” is substituted with 1 to 5 halogen atom(s). For example, trifluoromethylamino and the like are mentioned.

The “mono/di C_{2-6} alkenylamino” means an amino group, 1 or 2 hydrogen atom(s) of which is(are) substituted with a linear, branched, or cyclic “ C_{2-6} alkenyl group”. Specifically, vinylamino, allylamino, isopropenylamino, 2-methylallylamino, butenylamino, pentenylamino, hexenylamino, 1-cyclopropen-1-ylamino, 2-cyclopropen-1-ylamino, 1-cyclobuten-1-ylamino, 1-cyclopenten-1-ylamino, 2-cyclopenten-1-ylamino, 3-cyclopenten-1-ylamino, 1-cyclohexen-1-ylamino, 2-cyclohexen-1-ylamino, 3-cyclohexen-1-ylamino, 2,4-cyclopentadien-1-ylamino, 2,5-cyclohexadien-1-ylamino, divinylamino, diallylamino, diisopropenylamino, di(2-methylallyl)amino, dibutenylamino, dipentenylamino, dihexenylamino, di(1-cyclopropen-1-yl)amino, di(2-cyclopropen-1-yl)amino, di(1-cyclobuten-1-yl)amino, di(1-cyclopenten-1-yl)amino, di(2-cyclopenten-1-yl)amino, di(3-cyclopenten-1-yl)amino, di(1-cyclohexen-1-yl)amino, di(2-cyclohexen-1-yl)amino, di(3-cyclohexen-1-yl)amino, di(2,4-cyclopentadien-1-yl)amino, di(2,5-cyclohexadien-1-yl)amino, and the like are mentioned.

The “mono/di C_{2-6} alkynylamino” means an amino group, 1 or 2 hydrogen atom(s) of which is(are) substituted with a linear, branched, or cyclic “ C_{2-6} alkynyl group”. Specifically, ethynylamino, 1-propynylamino, 2-propynylamino, butynylamino, pentynylamino, hexynylamino, diethynylamino, di(1-propynyl)amino, di(2-propynyl)amino, dibutynylamino, dipentynylamino, dihexynylamino, and the like are mentioned.

The “ C_{2-7} alkanoylamino which is optionally substituted with $—OH$ or C_{1-6} alkoxy” means an amino group, a hydrogen atom of which is substituted with a linear, branched, or cyclic “ C_{2-7} alkanoyl group (the alkanoyl group is optionally substituted with $—OH$ or a C_{1-6} alkoxy group)”. Specifically, acetamide, propionamide, butylamide, isobutylamide, valeramide, isovaleramide, pivalamide, hexanamide, heptanamide, cyclopropanecarboxamide, cyclobutanecarboxamide, cyclopentanecarboxamide, cyclohexanecarboxamide, 2-me-

thylcyclopropanecarboxamide, hydroxyacetylamino, methoxyacetylamino, and the like are mentioned.

The “ C_{1-6} alkylsulfonylamino” means an amino group, a hydrogen atom of which is substituted with a linear, branched, or cyclic C_{1-6} alkylsulfonyl group. Specifically, methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino, cyclopropylsulfonylamino, cyclopropylmethylsulfonylamino, 2-methylcyclopropylsulfonylamino, and the like are mentioned.

The “arylcarbonylamino” means an amino group, a hydrogen atom of which is substituted with the “arylcarbonyl group”. Specifically, C_{6-14} arylcarbonylamino such as benzamide and naphthamide is mentioned.

The “heterocyclic carbonylamino” means an amino group, a hydrogen atom of which is substituted with the “heterocyclic carbonyl group”. Specifically, pyrrolicarboxamide, furancarboxamide, thiophenecarboxamide, imidazolecarboxamide, pyrazolecarboxamide, pyridinecarboxamide, indolecarboxamide, quinolinecarboxamide, piperidinecarboxamide, and the like are mentioned.

With regard to “ R^b and R^c optionally form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group” and “ R^{b1} and R^{c1} optionally form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group”, the 3- to 8-membered cyclic group specifically means, for example, a monovalent cyclic group obtained by removing a hydrogen atom which is bonded to a nitrogen atom from a ring that has a nitrogen atom in addition to carbon atoms in a 3- to 8-membered saturated or unsaturated non-aromatic heterocyclic group that is one of the “non-aromatic heterocyclic groups”. For example, aziridinyl, azetidiny, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, oxazolinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxadiazolinyl, oxadiazolidinyl, morpholinyl, thiomorpholinyl, 2-oxopyrrolidinyl, and the like are mentioned. As for R^b and R^c , and R^{b1} and R^{c1} , with regard to “where in the cyclic group, one carbon atom is substituted with an oxygen atom, a sulfur atom, or a carbonyl group”, examples of the cyclic group include, among the above-mentioned cyclic groups, oxazolinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, morpholinyl, thiomorpholinyl, and 2-oxopyrrolidinyl.

As for R^b and R^c , with regard to “where the nitrogen atom is substituted with a C_{1-6} alkyl group which is optionally substituted with 1 to 5 substituent(s) RI^1 ”, examples of the cyclic group include 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-propylpiperazin-1-yl, and 4-trifluoromethylpiperazin-1-yl.

As for R^{b1} and R^{c1} , with regard to “where the nitrogen atom is substituted with a C_{1-6} alkyl group”, examples of the cyclic group include 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, and 4-propylpiperazin-1-yl.

As for R^b and R^c , with regard to “where the cyclic group is further substituted with 1 to 5 substituent(s) RI^1 ”, examples of the cyclic group include 4,4-difluoropiperidin-1-yl.

The “substituent RI^1 ” is a group optionally selected from a halogen atom, $—OH$, a cyano group, a C_{1-6} alkoxy group (the C_{1-6} alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 $—OH$, 1 to 5 C_{1-6} alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 $—S(O)_iR^a$ (i is an integer of 0 to 2) group(s), 1 to 5 $—SO_2NR^dR^e$ group(s), 1 to 5 $—CONR^dR^e$ group(s), or 1 to 5 $—NR^{b1}R^{c1}$ group(s)), a $—NR^{b1}R^{c1}$ group, and a heterocyclic oxy group (the hetero-

25

cyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)).

The "substituent RI" is a group optionally selected from the same groups as in the case of the "substituent RI", a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group.

Here, R^a, R^d, R^e, R^{b1}, R^{c1}, and R^{e1} are the same as defined above as R^a, R^d, R^e, R^{b1}, R^{c1}, and R^{e1} respectively in the "—S(O)_iR^a group", the "—SO₂NR^dR^e group", the "—CONR^dR^e group", the "—CONR^dR^e group", and the "—NR^{b1}R^{c1} group".

The "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI" is a "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), and specific examples thereof include the following.

For example, a "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 halogen atom(s)" includes, in addition to the "C₁₋₆ alkyl group", a group in which the alkyl group is optionally substituted with 1 to 5 halogen atom(s). Specifically, in addition to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, for example, trifluoromethyl, trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, and the like are mentioned.

For example, a "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 —OH" includes, in addition to the "C₁₋₆ alkyl group", a group in which the alkyl group is optionally substituted with 1 to 5 hydroxy, and there are many regioisomers depending on a substitution position. Specifically, in addition to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxy-1-propyl, 2-hydroxy-1-propyl, 1-hydroxy-1-propyl, 2,3-dihydroxy-1-propyl, 1-hydroxy-1-methyl-1-ethyl, 2-hydroxy-1-methyl-1-ethyl, 4-hydroxy-1-butyl, 3-hydroxy-1-butyl, 2-hydroxy-1-butyl, 1-hydroxy-1-butyl, 3-hydroxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-2-hydroxymethylpropyl, 2-hydroxy-1,1-dimethyl-1-ethyl, 1-hydroxy-2-methylpropyl, 5-hydroxy-1-pentyl, 4-hydroxy-1-pentyl, 3-hydroxy-1-pentyl, 2-hydroxy-1-pentyl, 1-hydroxy-1-pentyl, 4-hydroxy-3-methylbutyl, 4-hydroxy-2-methylbutyl, 4-hydroxy-1-methylbutyl, 3-hydroxy-3-methylbutyl, 3-hydroxy-2-methylbutyl, 3-hydroxy-1-methylbutyl, 2-hydroxy-3-methylbutyl, 2-hydroxy-2-methylbutyl, 2-hydroxy-1-methylbutyl, 3-hydroxy-2,2-dimethylpropyl, 3-hydroxy-1,1-dimethylpropyl, 3-hydroxy-2-hydroxymethyl-2-

26

methylpropyl, 6-hydroxy-1-hexyl, 4-hydroxy-1,1-dimethyl-1-butyl, 4-hydroxy-3,3-dimethyl-1-butyl, 2-hydroxycyclopropyl, 4-hydroxycyclohexyl, and the like are mentioned.

For example, a "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 C₁₋₆ alkoxy group(s)" includes, in addition to the "C₁₋₆ alkyl group", a group in which the alkyl group is optionally substituted with 1 to 5 of the "C₁₋₆ alkoxy groups". Specifically, in addition to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, for example, methoxymethyl, methoxyethyl, methoxypropyl, ethoxyethyl, and the like are mentioned.

For example, a "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 C₁₋₆ alkoxy group(s) which is optionally substituted with 1 to 5 halogen atom(s)" includes, in addition to the "C₁₋₆ alkyl group" and the "C₁₋₆ alkyl group which is optionally substituted with 1 to 5 C₁₋₆ alkoxy group(s)", a group in which the alkyl group is optionally substituted with 1 to 5 of the "C₁₋₆ alkoxy groups" which is optionally substituted with 1 to 5 halogen atom(s). Specifically, in addition to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, methoxymethyl, methoxyethyl, and methoxypropyl, for example, trifluoromethoxymethyl, trifluoromethoxyethyl, trifluoromethoxypropyl, and the like are mentioned.

The alkyl group is optionally substituted with 2 to 5 groups optionally selected from two or more kinds of a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)). For example, a C₁₋₆ alkyl group which is substituted with one —OH and one C₁₋₆ alkoxy group, such as 2-hydroxy-3-methoxypropyl and 3-hydroxy-2-methoxypropyl, and the like are mentioned.

Similarly, the "C₂₋₆ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI" includes, in addition to the "C₂₋₆ alkenyl group", a group in which the alkenyl group is optionally substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)). Specifically, in addition to vinyl, allyl, isopropenyl, 2-methylallyl, butenyl, pentenyl, and hexenyl, for example, trifluorovinyl, 2-hydroxyvinyl, 2-methoxyvinyl, 2-trifluoromethoxyvinyl, and the like are mentioned.

The "C₂₋₆ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI" includes, in addition to the "C₂₋₆ alkynyl group", a group in which the alkynyl group is optionally substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5

halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)). Specifically, in addition to ethynyl, 1-propynyl, 2-propynyl, butynyl, pentynyl, and hexynyl, for example, fluoroethynyl, 2-hydroxyethynyl, 2-methoxyethynyl, 2-trifluoromethoxyethynyl, and the like are mentioned.

The “C₁₋₆ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI” includes, in addition to the “C₁₋₆ alkoxy group”, a group in which the alkoxy group is optionally substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —NR^{b1}R^{c1} group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s)), a —NR^{b1}R^{c1} group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)). Specifically, in addition to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and tert-butoxy, for example, trifluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-hydroxybutoxy, 3-hydroxy-3-methylbutoxy, 2,3-dihydroxypropoxy, 3-hydroxy-2-hydroxymethylpropoxy, 3-hydroxy-2-hydroxymethyl-2-methylpropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2-trifluoromethoxyethoxy, 2-methoxy-3-hydroxypropoxy, 2-hydroxy-3-methoxypropoxy, and the like are mentioned.

The “aryl group which is optionally substituted with 1 to 5 substituent(s) RII” is a group in which any hydrogen atom in the “aryl group” is optionally substituted with 1 to 5 substituent(s) RII. That is to say, the “aryl group which is optionally substituted with 1 to 5 substituent(s) RII” includes, in addition to the “aryl group”, an “aryl group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), and the like are mentioned.

group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{c1} group”.

Specifically, in addition to the “aryl group”, for example, an “aryl group which is optionally substituted with 1 to 5 halogen atom(s)”, an “aryl group which is substituted with 1 to 5 group(s) optionally selected from the “C₁₋₆ alkoxy group” (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”, an “aryl group which is substituted with 1 to 5 group(s) optionally selected from the “C₁₋₆ alkyl group” (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”, and the like are mentioned.

The aryl group is optionally substituted with 2 to 5 groups optionally selected from two or more kinds of a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{c1} group. Specifically, for example, an “aryl group which is optionally substituted with 1 or 2 of the “C₁₋₆ alkyl groups” and 1 or 2 of the “C₁₋₆ alkoxy groups” (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))” and the like are mentioned. More preferably, for example, an “aryl group which is optionally substituted with 1 or 2 of the “C₁₋₆ alkyl groups” and one of the “C₁₋₆ alkoxy group” (the C₁₋₆ alkoxy group is optionally substituted with 1 or 2 —OH, 1 or 2 C₁₋₆ alkoxy group(s), 1 or 2 non-aromatic heterocyclic group(s) (the heterocyclic group is optionally substituted with a C₁₋₆ alkyl group), 1 or 2 —S(O)_iR^a (i is an integer of 0 to 2) group(s), or 1 or 2 —NR^{b1}R^{c1} group(s))”, and the like are mentioned.

Examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" more specifically include, in addition to phenyl, (1- or 2-)naphthyl, indanyl, and tetrahydronaphthyl, (2-, 3-, or 4-)fluorophenyl, (2-, 3-, or 4-)chlorophenyl, (2,6-, 2,5-, 2,4-, 2,3-, or 3,5-)difluorophenyl, 4-chloro-2-fluorophenyl, (2-, 3-, or 4-)hydroxyphenyl, (2-, 3-, or 4-)cyanophenyl, (2,6-, 2,5-, 2,4-, 2,3-, 3,4-, or 3,5-)dicyanophenyl, (2-, 3-, or 4-)methoxyphenyl, (2-, 3-, or 4-)ethoxyphenyl, (2-, 3-, or 4-)propoxyphenyl, (2-, 3-, or 4-)isopropoxyphenyl, (2-, 3-, or 4-)trifluoromethoxyphenyl, (2-, 3-, or 4-)methylphenyl, (2-, 3-, or 4-)ethylphenyl, (2-, 3-, or 4-)propylphenyl, (2-, 3-, or 4-)isopropylphenyl, (2-, 3-, or 4-)isobutylphenyl, (2-, 3-, or 4-)tert-butylphenyl, (2-, 3-, or 4-)trifluoromethylphenyl, (2,6-, 2,5-, 2,4-, 2,3-, or 3,5-)dimethoxyphenyl, (2,6-, 2,5-, 2,4-, or 2,3-)dimethylphenyl, 3,5-difluoromethylphenyl, (4- or 5-)fluoro-(2- or 3-)methylphenyl, 3-fluoro-4-methylphenyl, 2-chloro-(4- or 5-)methylphenyl, (4- or 5-)fluoro-2-trifluoromethylphenyl, (4- or 5-)chloro-2-trifluoromethylphenyl, 2-(fluoro- or chloro)-5-trifluoromethylphenyl, (4- or 5-)fluoro-(2- or 3-)methoxyphenyl, 2-fluoro-(3-, 4-, or 5-)methoxyphenyl, (4- or 5-)chloro-(2- or 3-)methoxyphenyl, 2-chloro-(3-, 4-, or 5-)methoxyphenyl, (4- or 5-)fluoro-2-ethoxyphenyl, (4- or 5-)chloro-2-ethoxyphenyl, 3-(fluoro- or chloro)-4-ethoxyphenyl, 2-methoxy-5-methylphenyl, 4-methoxy-2-methylphenyl, 4-methoxy-(2,6-, 2,5-, or 2,3-)dimethylphenyl, (2-, 3-, or 4-)hydroxymethylphenyl, 4-cyano-3-hydroxymethylphenyl, (3- or 4)-(2-hydroxyethyl)phenyl, (3- or 4)-(2-hydroxy-3-methylbutoxy)phenyl, 4-(2-hydroxyethoxy)-2-methylphenyl, 4-(2,3-dihydroxypropoxy)-2-methylphenyl, 4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl, 3-(3-hydroxy-3-methylbutoxy)-2-methylphenyl, 4-(2-hydroxyethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-hydroxypropoxy)-2-methylphenyl, 4-(3-hydroxypropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2,3-dihydroxypropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((2R)-2,3-dihydroxypropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((2S)-2,3-dihydroxypropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-hydroxy-2-hydroxymethylpropoxy)-2-methylphenyl, 4-(3-hydroxy-2-hydroxymethyl-2-methylpropoxy)-2-methylphenyl, 4-(3-hydroxybutoxy)-2-methylphenyl, 4-((3S)-3-hydroxybutoxy)-2-methylphenyl, 4-((3R)-3-hydroxybutoxy)-2-methylphenyl, 4-(3-hydroxy-2-hydroxymethylpropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-hydroxy-2-hydroxymethyl-2-methylpropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((3S)-3-hydroxybutoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((3R)-3-hydroxybutoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-hydroxy-3-methylbutoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-aminopropoxy)-2-methylphenyl, 4-(3-aminopropoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-(2-oxo-1-pyrrolidinyl)ethoxy)-2-methylphenyl, 4-(2-(2-oxo-1-pyrrolidinyl)ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-(2-oxo-1-pyrrolidinyl)propoxy)-2-methylphenyl, 4-(3-(2-oxo-1-pyrrolidinyl)propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(5-oxo-2-pyrrolidinylmethoxy)-2-methylphenyl, 4-(5-oxo-2-pyrrolidinylmethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-ethoxyethoxy)-2-methylphenyl, 4-(2-ethoxyethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-methylsulfonyl-ethoxy)-2-methylphenyl, 4-(2-methylsulfonyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-methylsulfonyl-propoxy)phenyl, 4-(3-methylsulfonyl-propoxy)-2-methylphenyl, 4-(3-methylsulfonyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-2-methylphenyl, 4-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl,

4-((4-hydroxy-1,1-dioxidetetrahydro-2H-thiopyran-4-yl)methoxy)-2-methylphenyl, 4-((4-hydroxy-1,1-dioxidetetrahydro-2H-thiopyran-4-yl)methoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-((3-methyloxetan-3-yl)methoxy)-2-methylphenyl, 4-((3-methyloxetan-3-yl)methoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-acetylamino-ethoxy)-2-methylphenyl, 4-(2-acetylamino-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-acetylamino-propoxy)-2-methylphenyl, 4-(3-acetylamino-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-methylsulfonylamino-ethoxy)-2-methylphenyl, 4-(2-methylsulfonylamino-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-methylsulfonylamino-propoxy)-2-methylphenyl, 4-(3-methylsulfonylamino-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-carbamoyl-ethoxy)-2-methylphenyl, 4-(2-carbamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-carbamoyl-propoxy)-2-methylphenyl, 4-(3-carbamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-methylcarbamoyl-ethoxy)-2-methylphenyl, 4-(2-methylcarbamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-methylcarbamoyl-propoxy)-2-methylphenyl, 4-(3-methylcarbamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-dimethylcarbamoyl-ethoxy)-2-methylphenyl, 4-(2-dimethylcarbamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-dimethylcarbamoyl-propoxy)-2-methylphenyl, 4-(3-dimethylcarbamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-sulfamoyl-ethoxy)-2-methylphenyl, 4-(2-sulfamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-sulfamoyl-propoxy)-2-methylphenyl, 4-(3-sulfamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-methylsulfamoyl-ethoxy)-2-methylphenyl, 4-(2-methylsulfamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-methylsulfamoyl-propoxy)-2-methylphenyl, 4-(3-methylsulfamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(2-dimethylsulfamoyl-ethoxy)-2-methylphenyl, 4-(2-dimethylsulfamoyl-ethoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 4-(3-dimethylsulfamoyl-propoxy)-2-methylphenyl, 4-(3-dimethylsulfamoyl-propoxy)-(2,6-, 2,5-, or 2,3-)dimethylphenyl, 3-fluoro-4-(3-hydroxy-3-methylbutoxy)-2-methylphenyl, 3-fluoro-4-(3-hydroxy-3-methylbutoxy)-(2,6- or 2,5-)dimethylphenyl, 3-fluoro-4-(3-methylsulfonyl-propoxy)-2-methylphenyl, 3-fluoro-4-(3-methylsulfonyl-propoxy)-(2,6- or 2,5-)dimethylphenyl, 4-(3-hydroxy-3-methylbutoxy)-2-hydroxymethylphenyl, 4-(3-hydroxy-3-methylbutoxy)-6-methyl-2-hydroxymethylphenyl, 4-(3-methylsulfonyl-propoxy)-2-hydroxymethylphenyl, 4-(3-methylsulfonyl-propoxy)-6-methyl-2-hydroxymethylphenyl, (2-, 3-, or 4-)vinylphenyl, (2-, 3-, or 4-)acetylphenyl, (2-, 3-, or 4-)benzyloxyphenyl, 2-benzyloxy-(3-, 4-, 5-, or 6-)fluorophenyl, 4-benzyloxy-(2- or 3-)fluorophenyl, 4-benzyloxy-(2- or 3-)methylphenyl, (2-, 3-, or 4-)methylsulfonylphenyl, (2-, 3-, or 4-)carbamoylphenyl, (2-, 3-, or 4-)N-methylcarbamoylphenyl, (2-, 3-, or 4-)N,N-dimethylcarbamoylphenyl, (2-, 3-, or 4-)(N-(2-hydroxyethyl)carbamoyl)phenyl, (2-, 3-, or 4-)(N-(2-methoxyethyl)carbamoyl)phenyl, (2-, 3-, or 4-)(N-(2-hydroxyethyl)-N-methylcarbamoyl)phenyl, (2-, 3-, or 4-)(N-(2-methoxyethyl)-N-methylcarbamoyl)phenyl, (2-, 3-, or 4-)(N-(2-methylsulfonyl-ethyl)carbamoyl)phenyl, (2-, 3-, or 4-)(N-(2-methylsulfonyl-ethyl)-N-methylcarbamoyl)phenyl, 4-cyano-3-carbamoylphenyl, 3-cyano-4-carbamoylphenyl, (2-, 3-, or 4-)(pyrrolidine-1-yl)carbonylphenyl, (2-, 3-, or 4-)morpholinophenyl, 4-cyano-3-morpholinophenyl, (2-, 3-, or 4-)(2-oxooxazolidin-3-yl)phenyl, 4-cyano-3-(2-oxooxazolidin-3-yl)phenyl, (4-, 5-, 6-, or 7-)fluoro-1-indanyl, (4-, 5-, 6-, or 7-)chloro-1-indanyl, (4-, 5-, 6-, or 7-)bromo-1-indanyl, (4-, 5-, 6-, or 7-)trifluoromethyl-1-indanyl, (4-, 5-, 6-, or 7-)fluoro-2-indanyl, (4-, 5-, 6-, or 7-)chloro-2-indanyl,

(4-, 5-, 6-, or 7-)bromo-2-indanyl, (4-, 5-, 6-, or 7-)trifluoromethyl-2-indanyl, (2-, 3-, 4-, 5-, 6-, 7-, or 8-)fluoro-naphthalene-1-yl, (2-, 3-, 4-, 5-, 6-, 7-, or 8-)chloro-naphthalene-1-yl, and (2-, 3-, 4-, 5-, 6-, 7-, or 8-)methyl-naphthalene-1-yl.

The “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” is a group in which any hydrogen atom in the “heterocyclic group” is optionally substituted with 1 to 5 substituent(s) RII. Namely, the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” is, in addition to the unsubstituted “heteroaryl group” and the “non-aromatic heterocyclic group” both exemplified above as a “heterocyclic group” (these rings are each a monovalent group obtained by removing any hydrogen atom from a ring having a monocyclic ring or a fused ring that is a 3- to 14-membered ring, or preferably a 3- to 12-membered ring, containing, in addition to carbon atoms, at least one hetero atom (preferably 1 to 4 atom(s)) optionally selected from N, O, and S): a “heterocyclic group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group”.

Specific examples of the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” include, in addition to the “heterocyclic group”, a “heterocyclic group optionally substituted with 1 to 5 halogen atom(s)”, a “heterocyclic group substituted with 1 to 5 group(s) optionally selected from the “C₁₋₆ alkoxy group” (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”, and a “heterocyclic group substituted with 1 to 5 group(s) optionally selected from the “C₁₋₆ alkyl group” (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”. More specific examples thereof include a “heteroaryl group substituted with 1 to 5 group(s) optionally selected from the “C₁₋₆ alkyl group” (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1

to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))” and a “heteroaryl group substituted with 1 to 5 groups(s) optionally selected from the “C₁₋₆ alkoxy group” (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”.

Furthermore, the heterocyclic group is optionally substituted with 2 to 5 groups optionally selected from 2 or more kinds of a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group. Specific examples thereof include a “heterocyclic group optionally substituted with 1 or 2 “C₁₋₆ alkyl group(s)” and 1 or 2 “C₁₋₆ alkoxy group(s)” (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s))”. More preferred examples thereof include a “heteroaryl group optionally substituted with 1 or 2 “C₁₋₆ alkyl group(s)” and one “C₁₋₆ alkoxy group” (the C₁₋₆ alkoxy group is optionally substituted with 1 or 2 —OH, 1 or 2 C₁₋₆ alkoxy group(s), 1 or 2 non-aromatic heterocyclic group(s) (the heterocyclic group is optionally substituted with a C₁₋₆ alkyl group), 1 or 2 —S(O)_iR^a (i is an integer of 0 to 2) group(s), or 1 or 2 —NR^{b1}R^{c1} group(s))”.

The “heteroaryl group” in the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” may be monocyclic or ring-fused. The monocyclic heteroaryl group preferably has a 5- to 7-membered ring, and examples thereof include those groups described in the definition of the “heteroaryl group”, such as pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl,

pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2H-1,2,3-thiadiazinyl, 4H-1,2,4-thiadiazinyl, 6H-1,3,4-thiadiazinyl, 1,4-diazepinyl, and 1,4-oxazepinyl. The ring-fused heteroaryl group preferably has an 8- to 14-membered ring, and examples thereof include a monovalent group obtained by removing any hydrogen atom from a fused ring formed by fusing the 5- to 7-membered heterocyclic ring and a monocyclic aryl group (such as a benzene ring) or a monocyclic heteroaryl group. The hydrogen atom is optionally removed from any of the fused rings. Specific examples include those groups described in the definition of the "heteroaryl group", such as indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzimidazolyl, 1H-indazolyl, 1H-benzotriazolyl, 2,1,3-benzothiadiazinyl, chromenyl, isochromenyl, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, quinolyl, isoquinolyl, cinnolyl, quinazolyl, quinoxalyl, phthalazinyl, benzoxazepinyl, benzoazepinyl, benzodiazepinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizyl, thieno[3,2-c]pyridyl, thiazolo[5,4-c]pyridyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,5-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, 1H-pyrazolo[3,4-b]pyridyl, 1,2,4-triazolo[1,5-a]pyrimidinyl, and dibenzofuranyl. Specific examples thereof also include a ring-fused heteroaryl group which is partly hydrogenated, such as indolinyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, chromanyl, isochromanyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, tetrahydroquinoxalyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, tetrahydrobenzoxazepinyl, tetrahydrobenzoazepinyl, and 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridyl. The ring-fused heteroaryl group which is partly hydrogenated preferably has an 8- to 12-membered ring, namely a monovalent group obtained by removing any hydrogen atom from a fused ring which is partly hydrogenated and formed by fusing the 5- to 7-membered heterocyclic ring and a monocyclic aryl group (such as a benzene ring) or a monocyclic heteroaryl group. Any of the hydrogen atom in the aryl group or in the heterocyclic moiety and of the hydrogen atom in the hydrogenated moiety is optionally removed. In the case of tetrahydroquinolyl, examples of the partly hydrogenated ring-fused heteroaryl group include 5,6,7,8-tetrahydroquinolyl and 1,2,3,4-tetrahydroquinolyl. Depending on the position in these groups from which any hydrogen atom is removed, -2-yl, -3-yl, -4-yl, -5-yl, -6-yl, -7-yl, and -8-yl are exemplified in the case of 5,6,7,8-tetrahydroquinolyl, and in the case of 1,2,3,4-tetrahydroquinolyl, -1-yl, -2-yl, -3-yl, -4-yl, -5-yl, -6-yl, -7-yl, and -8-yl are exemplified.

Examples of the "non-aromatic heterocyclic group" in the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" include a 3- to 8-membered saturated or unsaturated non-aromatic heterocyclic group. Specific examples thereof include aziridinyl, azetidiny, oxiranyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, pyrazolinyl, pyrazolidinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl (oxanyl), tetrahydrothiopyranyl, piperazinyl, dioxanyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolidinyl, isothiazolidinyl, oxadiazolyl, oxadiazolidinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, and oxepanyl. The "non-aromatic

heterocyclic group" means a monovalent group obtained by removing any hydrogen atom from the ring.

Specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" include pyrrolyl, furyl, thienyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidinyl, indolyl, 1H-benzimidazolyl, quinolyl, dibenzofuranyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, chromanyl, 1,3-benzodioxanyl, 1,4-benzodioxanyl, piperidinyl, dihydropyranyl, and tetrahydropyranyl (oxanyl). Further specific examples thereof include 2-pyrrolyl, 3-pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl, 1H-benzimidazol-1-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-4-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-7-yl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl, 1-dibenzofuranyl, 2-dibenzofuranyl, 3-dibenzofuranyl, 4-dibenzofuranyl, 1,4-benzodioxazine-2-yl, 1,4-benzodioxazine-3-yl, 1,4-benzodioxazine-5-yl, 1,4-benzodioxazine-6-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 3,6-dihydro-2H-pyran-4-yl, and 4-tetrahydropyranyl (4-oxanyl). Any hydrogen atom of the groups is optionally substituted with 1 to 5 substituent(s) RII. Specific examples thereof include (3-, 4-, or 5-)chlorothiophen-2-yl, (2-, 4-, or 5-)chlorothiophen-3-yl, (3-, 4-, or 5-)acetylthiophen-2-yl, 1-methylpyrazol-4-yl, 3,5-dimethylisoxazol-4-yl, (2-, 4-, 5-, or 6-)fluoropyridin-3-yl, (2-, 4-, 5-, or 6-)chloropyridin-3-yl, (2-, 4-, 5-, or 6-)hydroxypyridin-3-yl, (3-, 4-, 5-, or 6-)cyanopyridin-2-yl, (2-, 4-, 5-, or 6-)cyanopyridin-3-yl, (2- or 3-)cyanopyridin-4-yl, (3-, 4-, 5-, or 6-)methoxypyridin-2-yl, (2-, 4-, 5-, or 6-)methoxypyridin-3-yl, (2- or 3-)methoxypyridin-4-yl, (2-, 4-, 5-, or 6-)ethoxypyridin-3-yl, (2-, 4-, 5-, or 6-)cyclopropylmethoxypyridin-3-yl, (3-, 4-, 5-, or 6-)methylpyridin-2-yl, (2-, 4-, 5-, or 6-)methylpyridin-3-yl, (2- or 3-)methylpyridin-4-yl, (2-, 4-, 5-, or 6-)trifluoromethylpyridin-3-yl, 6-(3-hydroxybutoxy)pyridin-3-yl, 6-(3-hydroxy-3-methylbutoxy)pyridin-3-yl, 6-(2-ethoxyethoxy)pyridin-3-yl, 6-(3-methylsulfonylpropoxy)pyridin-3-yl, (2,4-, 2,5-, 2,6-, 4,5-, 4,6-, or 5,6-)dimethylpyridin-3-yl, (2,4-, 2,5-, 2,6-, 4,5-, 4,6-, or 5,6-)dimethoxypyridin-3-yl, 6-isopropyl-(2-, 4-, or 5-)chloropyridin-3-yl, 6-methoxy-(2-, 4-, or 5-)methylpyridin-3-yl, 6-(2-hydroxyethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-hydroxypropoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2,3-dihydroxypropoxy)-(2- or 4-)methylpyridin-3-yl, 6-((2R)-2,3-dihydroxypropoxy)-(2- or 4-)methylpyridin-3-yl, 6-((2S)-2,3-dihydroxypropoxy)-(2- or 4-)methylpyridin-3-yl, 6-((3S)-3-hydroxybutoxy)-(2- or 4-)methylpyridin-3-yl, 6-((3R)-3-hydroxybutoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-hydroxy-3-methylbutoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-hydroxy-2-hydroxymethylpropoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-hydroxy-2-hydroxymethyl-2-methylpropoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-hydroxybutoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-ethoxyethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-methylsulfonylethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-methylsulfonylpropoxy)-(2- or 4-)methylpyridin-3-yl, 6-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-(2- or 4-)methylpyridin-3-yl, 6-((4-hydroxy-1,1-dioxidetetrahydro-2H-thiopyran-4-yl)methoxy)-(2- or 4-)methylpyridin-3-yl, 6-((3-methyloxetane-3-yl)methoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-hydroxyethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxypropoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2,3-dihydroxypropoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxy-2-hy-

35

droxymethylpropoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxy-2-hydroxymethyl-2-methylpropoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxybutoxy)-(2, 4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxy-3-methylbutoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-ethoxyethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-methylsulfonylethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-methylsulfonyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-((4-hydroxy-1,1-dioxidetetrahydro-2H-thiopyran-4-yl) methoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-((3-methyloxetane-3-yl)methoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-hydroxy-3-methylbutoxy)-(2- or 4-)methoxypyridin-3-yl, 6-(2-aminoethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-aminoethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-aminopropoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-aminopropoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-acetylamino-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-acetylamino-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-acetylamino-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-acetylamino-propoxy)-(2, 4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-methylsulfonylamino-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-methylsulfonylamino-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-methylsulfonylamino-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-methylsulfonylamino-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-carbamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-carbamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-carbamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-carbamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-methylcarbamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-methylcarbamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-methylcarbamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-methylcarbamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-dimethylcarbamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-dimethylcarbamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-dimethylcarbamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-dimethylcarbamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-sulfamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-sulfamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-sulfamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-sulfamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-methylsulfamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-methylsulfamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-methylsulfamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-methylsulfamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-dimethylsulfamoyl-ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-dimethylsulfamoyl-ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-dimethylsulfamoyl-propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-dimethylsulfamoyl-propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(2-(2-oxo-1-pyrrolidinyl)ethoxy)-(2- or 4-)methylpyridin-3-yl, 6-(2-(2-oxo-1-pyrrolidinyl)ethoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(3-(2-oxo-1-pyrrolidinyl)propoxy)-(2- or 4-)methylpyridin-3-yl, 6-(3-(2-oxo-1-pyrrolidinyl)propoxy)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-(1-piperidinyl)pyridin-3-yl, 6-(4-morpholino)pyridin-3-yl, 6-(4-morpholino)-(2,4-, 2,5-, or 4,5-)dimethylpyridin-3-yl, 6-acetylpyridin-3-yl, 6-benzoyloxy-pyridin-3-yl, 6-methylsulfonylpyridin-3-yl, 6-carbamoylpyridin-3-yl, (2- or 4-)methoxypyrimidin-5-yl, 2-(3-hydroxy-3-methylbutoxy)-4-methylpyrimidin-5-yl, 2-(3-methylsulfonyl-propoxy)-4-methylpyrimidin-5-yl,

36

2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl, 2-(3-methylsulfonyl-propoxy)-4,6-dimethylpyrimidin-5-yl, 2-(4-morpholino)-4,6-dimethylpyrimidin-5-yl, 2-ethyl-6, 7-difluoro-1H-benzimidazol-1-yl, 2-ethoxy-6,7-difluoro-1H-benzimidazol-1-yl, (2-, 4-, 5-, 6-, 7-, or 8-) methylquinoline-3-yl, 6-(1-piperidinyl)pyridin-3-yl, 1-methylpiperidin-4-yl, and 4,4-difluoropiperidin-1-yl.

The “aralkyl group which is optionally substituted with 1 to 5 substituent(s) R^{II}” is the “aralkyl group” in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) R^{II}. That is to say, the “aralkyl group which is optionally substituted with 1 to 5 substituent(s) R^{II}” includes, in addition to the unsubstituted groups exemplified as the “aralkyl group”: “an aralkyl group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group”. The substituent(s) of the aralkyl group may be substituted with either the aryl moiety or the alkyl moiety. Specific examples thereof include, in addition to unsubstituted benzyl, phenethyl, 1-naphthylmethyl, or 2-naphthylmethyl: (2-, 3-, or 4-)fluorobenzyl, (2-, 3-, or 4-)chlorobenzyl, (2-, 3-, or 4-)hydroxybenzyl, (2-, 3-, or 4-)methoxybenzyl, (2-, 3-, or 4-)trifluoromethoxybenzyl, (2-, 3-, or 4-)methylbenzyl, (2-, 3-, or 4-)trifluoromethylbenzyl, (2,6-, 2,5-, 2,4-, or 2,3-)dimethylbenzyl, 3,5-ditrifluoromethylbenzyl, 4-(2-hydroxyethoxy)-2,6-dimethylbenzyl, 4-(2,3-dihydroxypropoxy)-2,6-dimethylbenzyl, and 4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylbenzyl.

The “heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) R^{II}” is the “heteroarylalkyl group” in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) R^{II}. That is to say, the “heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) R^{II}” includes, in addition to the unsubstituted groups exemplified as the “heteroarylalkyl group”: “a heteroarylalkyl group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5

—NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group". The substituent(s) of the heteroarylalkyl group may be substituted with either the heteroaryl moiety or the alkyl moiety. Specific examples thereof include, in addition to unsubstituted pyrrolidylmethyl, furylmethyl, pyridylmethyl, or quinolylmethyl: (2-, 4-, 5-, or 6-)chloropyridin-3-ylmethyl, (2-, 4-, 5-, or 6-)hydroxypyridin-3-ylmethyl, (2-, 4-, 5-, or 6-)methoxypyridin-3-ylmethyl, (2-, 4-, 5-, or 6-)methylpyridin-3-ylmethyl, (2,4-, 2,5-, 2,6-, 4,5-, or 4,6-)dimethylpyridin-3-ylmethyl, 6-(2-hydroxyethoxy)-2,4-dimethylpyridin-3-ylmethyl, 6-(2,3-dihydroxypropoxy)-2,4-dimethylpyridin-3-ylmethyl, and 6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-ylmethyl.

The "non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII" is the "non-aromatic heterocyclic alkyl group" in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) RII. That is to say, the "non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII" includes, in addition to the unsubstituted groups exemplified as the "non-aromatic heterocyclic alkyl group": "a non-aromatic heterocyclic alkyl group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), or 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group". The substituent(s) of the non-aromatic heterocyclic alkyl group may be substituted with either the non-aromatic heterocyclic moiety or the alkyl moiety. Specific examples thereof include, in addition to unsubstituted pyrrolidinylmethyl, tetrahydrofurylmethyl, piperidinylmethyl, or tetrahydropyranylmethyl: (2-, 3-, or 4-)chloropiperidin-1-ylmethyl, (2-, 3-, or 4-)hydroxypiperidin-1-ylmethyl, (2-, 3-, or 4-)cy-

anopiperidin-1-ylmethyl, (2-, 3-, or 4-)methoxypiperidin-1-ylmethyl, (2-, 3-, or 4-)methylpiperidin-1-ylmethyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)dimethylpiperidin-1-ylmethyl, 4-(2-hydroxyethoxy)-2,6-dimethylpiperidin-1-ylmethyl, 4-(2,3-dihydroxypropoxy)-2,6-dimethylpiperidin-1-ylmethyl, and 4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylpiperidin-1-ylmethyl.

The "aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII" is the "aryloxy group" in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) RII. The "aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII" is also the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" which is substituted with an oxygen atom. That is to say, the "aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII" includes, in addition to the unsubstituted groups exemplified as the "aryloxy group": "an aryloxy group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group". Specific examples thereof include a group in which the group exemplified specifically as the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" is substituted with an oxygen atom, such as, in addition to unsubstituted phenoxy, 1-naphthyl, 2-naphthyl, 1-indanyl, or 2-indanyl: (2-, 3-, or 4-)fluorophenoxy, (2-, 3-, or 4-)chlorophenoxy, (2-, 3-, or 4-)hydroxyphenoxy, (2-, 3-, or 4-)cyanophenoxy, (2-, 3-, or 4-)methoxyphenoxy, (2-, 3-, or 4-)trifluoromethoxyphenoxy, (2-, 3-, or 4-)methylphenoxy, (2-, 3-, or 4-)trifluoromethylphenoxy, (2,6-, 2,5-, 2,4-, or 2,3-)dimethylphenoxy, (3- or 4-)(2-hydroxyethyl)phenoxy, 4-(2-hydroxyethoxy)phenoxy, 4-(2,3-dihydroxypropoxy)phenoxy, (3- or 4-)(3-hydroxy-3-methylbutoxy)phenoxy, (3- or 4-)(2-ethoxy-ethoxy)phenoxy, (3- or 4-)(3-methylsulfonyl-propoxy)phenoxy, 4-(3-hydroxy-3-methylbutoxy)-2-methylphenoxy, 4-(2-ethoxy-ethoxy)-2-methylphenoxy, 4-(3-methylsulfonyl-propoxy)-2-methylphenoxy, 4-(2-hydroxyethoxy)-2,6-dimethylphenoxy, 4-(2,3-dihydroxypropoxy)-2,6-dimethylphenoxy, 4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenoxy, 4-(2-ethoxy-ethoxy)-2,6-dimethylphenoxy, 4-(3-methylsulfonyl-propoxy)-2,6-dimethylphenoxy, 4-methylsulfonylphenoxy, and 4-(4-morpholino)phenoxy.

The "heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII" is the "heteroaryloxy group" in

which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) RII. The “heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII” is also a group in which a group having the “heteroaryl group” in the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” is substituted with an oxygen atom. That is to say, the “heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII” includes, in addition to the unsubstituted groups exemplified as the “heteroaryloxy group”: “a heteroaryloxy group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group”. Specific examples thereof include a group in which a group having the “heteroaryl group” among the groups exemplified specifically as the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII” is substituted with an oxygen atom, such as, in addition to pyrroloxy, furyloxy, thienyloxy, (2-, 3-, or 4-)pyridyloxy, pyrimidinylloxy, or quinolyloxy: (2-, 4-, 5-, or 6-)chloropyridin-3-yloxy, (2- or 3-)chloropyridin-4-yloxy, (2-, 4-, 5-, or 6-)hydroxypyridin-3-yloxy, (2- or 3-)hydroxypyridin-4-yloxy, (3-, 4-, 5-, or 6-)cyanopyridin-2-yloxy, (2-, 4-, 5-, or 6-)cyanopyridin-3-yloxy, (2- or 3-)cyanopyridin-4-yloxy, (2-, 4-, 5-, or 6-)methoxypyridin-3-yloxy, (2- or 3-)methoxypyridin-4-yloxy, (2-, 4-, 5-, or 6-)methylpyridin-3-yloxy, (2- or 3-)methylpyridin-4-yloxy, (2,4-, 2,5-, 2,6-, 4,5-, or 4,6-)dimethylpyridin-3-yloxy, (2,3-, 2,5-, 2,6-, or 3,5-)dimethylpyridin-4-yloxy, 6-methoxy-(2-, 4-, or 5-)methylpyridin-3-yloxy, 6-(2-hydroxyethoxy)pyridin-3-yloxy, 6-(2,3-dihydroxypropoxy)pyridin-3-yloxy, 6-(3-hydroxy-3-methylbutoxy)pyridin-3-yloxy, 6-(2-ethoxyethoxy)pyridin-3-yloxy, 6-(3-methylsulfonyl-propoxy)pyridin-3-yloxy, 6-(3-hydroxy-3-methylbutoxy)-(2- or 4-)methylpyridin-3-yloxy, 6-(2-ethoxyethoxy)-(2- or 4-)methylpyridin-3-yloxy, 6-(3-methylsulfonyl-propoxy)-(2- or 4-)methylpyridin-3-yloxy, 6-(2-hydroxyethoxy)-2,4-dimethylpyridin-3-yloxy, 6-(2,3-dihydroxypropoxy)-2,4-dimethylpyridin-3-yloxy, 6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yloxy, 6-(2-ethoxyethoxy)-2,4-dimethylpyridin-3-yloxy, 6-(3-methylsulfonyl-propoxy)-2,4-dimethylpyridin-3-yloxy, and 6-(4-morpholino)pyridin-3-yloxy.

The “non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII” is the “non-aromatic heterocyclic oxy group” in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s)

RII. That is to say, the “non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII” includes, in addition to the unsubstituted groups exemplified as the “non-aromatic heterocyclic oxy group”: “a non-aromatic heterocyclic oxy group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group”. For example, a 3- to 8-membered saturated or unsaturated non-aromatic heterocyclic oxy group optionally substituted with 1 to 5 substituent(s) RII is included. Examples thereof include, in addition to pyrrolidinylloxy, tetrahydrofuryloxy, piperidinylloxy, dihydropyranyloxy, or tetrahydropyranyloxy (oxanyloxy): (2- or 3-)fluorooxane-4-yloxy, (2- or 3-)chlorooxane-4-yloxy, (2- or 3-)hydroxyoxane-4-yloxy, (2- or 3-)methoxyoxane-4-yloxy, (2- or 3-)trifluoromethoxyoxane-4-yloxy, (2- or 3-)methyloxane-4-yloxy, (2- or 3-)trifluoromethyloxane-4-yloxy, (2,3-, 2,5-, 2,6-, or 3,5-)dimethyloxane-4-yloxy, 1-methylpiperidin-4-yloxy, and (1,2- or 1,3-)dimethylpiperidin-4-yloxy.

The “aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII” is the “aralkyloxy group” in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) RII. That is to say, the “aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII” includes, in addition to the unsubstituted groups exemplified as the “aralkyloxy group”: “an aralkyloxy group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the hetero-

41

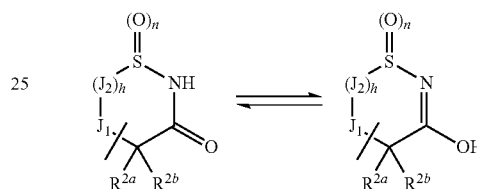
cyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1} group”. The substituent(s) of the aralkyloxy group may be substituted with the aryl moiety or the alkyl moiety. Specific examples thereof include, in addition to benzyloxy, phenethyloxy, 1-naphthylmethoxy, or 2-naphthylmethoxy: (2-, 3-, or 4-)fluorobenzyloxy, (2-, 3-, or 4-)chlorobenzyloxy, (2-, 3-, or 4-)hydroxybenzyloxy, (2-, 3-, or 4-)methoxybenzyloxy, (2-, 3-, or 4-)trifluoromethoxybenzyloxy, (2-, 3-, or 4-)methylbenzyloxy, (2-, 3-, or 4-)trifluoromethylbenzyloxy, (2-, 3-, or 4-)methoxyphenethyloxy, (2,6-, 2,5-, 2,4-, or 2,3-)dimethylbenzyloxy, 4-(2-hydroxyethoxy)-2,6-dimethylbenzyloxy, 4-(2,3-dihydroxypropoxy)-2,6-dimethylbenzyloxy, and 4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylbenzyloxy.

The “heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII” is the “heteroarylalkyloxy group” in which any hydrogen atom is optionally substituted with 1 to 5 substituent(s) RII. That is to say, the “heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII” includes, in addition to the unsubstituted groups exemplified as the “heteroarylalkyloxy group”: “a heteroarylalkyloxy group which is substituted with 1 to 5 group(s) optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3

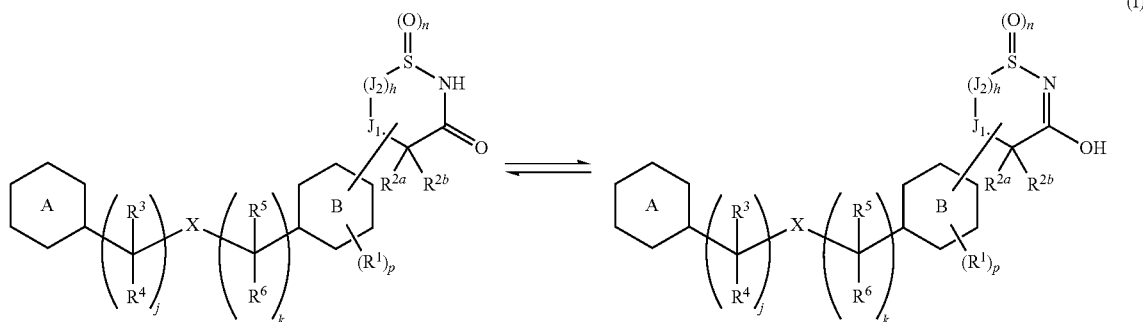
42

group”. The substituent(s) of the heteroarylalkyloxy group may be substituted with either the heteroaryl moiety or the alkyl moiety. Specific examples thereof include, in addition to pyrrolylmethoxy, furylmethoxy, pyridylmethoxy, or quinolylmethoxy: (2-, 4-, 5-, or 6-)chloropyridin-3-ylmethoxy, (2-, 4-, 5-, or 6-)hydroxypyridin-3-ylmethoxy, (2-, 4-, 5-, or 6-)methoxypyridin-3-ylmethoxy, (2-, 4-, 5-, or 6-)methylpyridin-3-ylmethoxy, (2,4-, 2,5-, 2,6-, 4,5-, or 4,6-)dimethylpyridin-3-ylmethoxy, 6-(2-hydroxyethoxy)-2,4-dimethylpyridin-3-ylmethoxy, 6-(2,3-dihydroxypropoxy)-2,4-dimethylpyridin-3-ylmethoxy, and 6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-ylmethoxy.

In the compound of Formula (I), in the cyclic amide structure moiety, proton tautomerism shown by the formula below can be generated. The abundance ratio of this structure can vary depending on whether the compound of Formula (I) is in the solid state or in the dissolved state in a liquid. The tautomer generated by the cyclic amide moiety is included in Formula (I).

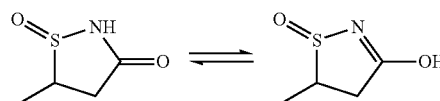


Namely, in Formula (I), for example, a proton tautomer as shown below is supposed and such a tautomer is also included in the range of the present compound.



oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a —NR^{b1}R^{c1} group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^dR^{e1}

For example, when in the cyclic amide structure of Formula (I), n is 1, h is 0, J₁ is CR^{11a}, R^{2a}, R^{2b}, and R^{11a} are a hydrogen atom, and the ring B is bonded to J₁, the tautomerism as shown below is supposed and such a tautomer is also included in the range of the present compound.



The description of any specific types of tautomers in any structural formulae of the present specification is not intended to limit the present invention, but is intended to represent the whole set of tautomers that are applicable.

Specifically, for example, a tautomer, namely, 5-[4-[[3-[4-(2-ethoxyethoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-2-isothiazoline-3-ol, of the compounds described as 5-[4-[[3-[4-(2-ethoxyethoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one among compounds of Example 1 is also categorized as a compound of Example 1. In addition, a tautomer, namely, 5-(4-((3-(2,6-dimethyl-4-(2-ethoxyethoxy)phenyl)phenyl)methoxy)phenyl)-4-isothiazoline-3-one 1-oxide, of the compounds described as 5-(4-((3-(2,6-dimethyl-4-(2-ethoxyethoxy)phenyl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide among compounds of Step 6 of Example 1, which are a reaction intermediate, is also categorized as a compound of Step 6 of Example 1.

[1-1] In the compound of Formula (I) according to Aspect [1], Ls are independently a group optionally selected from a halogen atom, —OH, an oxo group, a cyano group, a C₁₋₁₀ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₁₀ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, —SH, —SF₅, a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^bR^c group, and a substituted spiropiperidinylmethyl group; and

the substituent(s) RI, the substituent(s) RII, i, R^a, R^b, and R^c are the same as defined in Aspect [1].

[1-1-a] Preferable examples of Ls include a group optionally selected from a halogen atom, a cyano group, a C₁₋₁₀ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₁₀ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkynyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII,

an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a —NR^bR^c group, and a substituted spiropiperidinylmethyl group (the substituent(s) RI and the substituent(s) RII are the same as defined in Aspect [1]).

[1-1-b] More preferable examples of Ls include a group optionally selected from a halogen atom, a cyano group, a C₁₋₁₀ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₁₀ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a —NR^bR^c group, and a substituted spiropiperidinylmethyl group (the substituent(s) RI and the substituent(s) RII are the same as defined in Aspect [1]).

[1-1-c] Further preferable examples of Ls include a group optionally selected from a halogen atom, a cyano group, a C₁₋₁₀ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₁₀ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₁₀ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, and a substituted spiropiperidinylmethyl group (the substituent(s) RI and the substituent(s) RII are the same as defined in Aspect [1]).

[1-1-d] Most preferable examples of Ls include a group optionally selected from a halogen atom, a cyano group, a C₁₋₁₀ alkyl group (the C₁₋₁₀ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₂₋₁₀ alkenyl group (the C₂₋₁₀ alkenyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₁₋₁₀ alkoxy group (the C₁₋₁₀ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₂₋₁₀ alkenyloxy group (the C₂₋₁₀ alkenyloxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), an aryl group which is optionally substituted with 1 to 5 substituent(s) RIIa, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RIIa, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RIIa, a non-aromatic

heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, and a substituted spiroperidinylmethyl group (the substituent(s) RIIa are the same as or different from each other and are each a group optionally selected from a halogen atom, a cyano group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s), 1 to 5 non-aromatic heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 or 2 C₁₋₄ alkyl group(s) or 1 or 2 oxo group(s)), or 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s)), a —NR^bR^{c1} group, a non-aromatic heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 or 2 oxo group(s)), a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₂₋₆ alkenyl group, a C₂₋₇ alkanoyl group, an aralkyloxy group, a non-aromatic heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 2 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —CONR^dR^e group, and a —CONR^{d3}R^{e3} group (R^{d3} is a hydrogen atom or a C₁₋₄ alkyl group; and R^{e3} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 group(s) optionally selected from —OH, a C₁₋₆ alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C₁₋₄ alkyl group(s) or 1 to 2 oxo group(s)), and a —S(O)_iR^a (i is an integer of 0 to 2) group))), Substitution with one to three substituent(s) RIIa is preferable.

More specific examples of Ls include the groups specifically exemplified above as the “halogen atom”, the “C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI”, the “C₁₋₆ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI”, the “aryl group which is optionally substituted with 1 to 5 substituent(s) RII”, the “heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII”, the “aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII”, the “heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII”, the “non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII”, the “aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII”, the “heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII”, the “non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII”, the “aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII”, the “heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII”, the substituted spiroperidinylmethyl group”, and the like.

[1-2] In the compound of Formula (I) according to Aspect [1], R¹s are independently a group optionally selected from a halogen atom, a C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₆ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI (the substituents RII are the same as or different from each other and are the same as defined as the substituent(s) RI above), and a cyano group.

[1-2-a] Preferable examples of R¹s include a halogen atom, a C₁₋₄ alkyl group which is optionally substituted with 1 to 5

substituent(s) RI, a C₁₋₄ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI (the substituents RII are the same as or different from each other and are the same as defined as the substituent(s) RI above), and a cyano group.

[1-2-b] More preferable examples of R¹s include a halogen atom, a C₁₋₄ alkyl group which is optionally substituted with 1 to 5 halogen atom(s), a C₁₋₄ alkoxy group which is optionally substituted with 1 to 5 halogen atom(s), and a cyano group. Specific examples of R¹ include a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, trifluoromethoxy, and cyano.

[1-3] In the compound of Formula (I) according to Aspect [1], R^{2a} and R^{2b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, and a cyano group.

[1-3-a] Preferable examples of R^{2a} and R^{2b} independently include a hydrogen atom, a halogen atom, and a C₁₋₄ alkyl group, and specific examples thereof include a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, and methyl.

[1-3-b] More preferably, any one of R^{2a} and R^{2b} is a hydrogen atom, and further preferably, both of R^{2a} and R^{2b} are each a hydrogen atom.

[1-4] In the compound of Formula (I) according to Aspect [1], R³, R⁴, R⁵, R⁶, and R⁷ are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, and a C₂₋₆ alkynyl group.

[1-4-a] R³, R⁴, R⁵, R⁶, and R⁷ are preferably a hydrogen atom.

[1-5] In the compound of Formula (I) according to Aspect [1], R^{11a} and R^{11b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, a halogenated C₁₋₆ alkoxy group, a C₂₋₇ alkanoyl group, and a carboxy group which is optionally protected.

[1-5-a] Preferable examples of R^{11a} and R^{11b} independently include a hydrogen atom, a halogen atom, a C₁₋₄ alkyl group, a halogenated C₁₋₄ alkyl group, a C₂₋₅ alkanoyl group, and a carboxy group. More specifically, R^{11a} and R^{11b} are independently a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, acetyl, carboxy, or the like, more preferably a hydrogen atom.

[1-6] In the compound of Formula (I) according to Aspect [1], R^{12a} and R^{12b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a halogenated C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₁₋₆ alkoxy group, a halogenated C₁₋₆ alkoxy group, and a cyano group.

[1-6-a] Preferable examples of R^{12a} and R^{12b} independently include a hydrogen atom, a halogen atom, a C₁₋₄ alkyl group, a halogenated C₁₋₄ alkyl group, and a cyano group. Specifically, R^{12a} and R^{12b} are a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, cyano, or the like.

[1-6-b] More preferably, any one of R^{12a} and R^{12b} is a hydrogen atom, and further preferably, both of R^{12a} and R^{12b} are each a hydrogen atom.

[1-7] In the compound of Formula (I) according to Aspect [1], R^{11c} and R^{12c} are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, and a halogenated C₁₋₆ alkyl group.

[1-7-a] Preferable examples of R^{11c} and R^{12c} independently include a hydrogen atom and a C_{1-4} alkyl group. More specifically, R^{11c} and R^{12c} are independently a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, or the like. More preferably, R^{11c} and R^{12c} are each a hydrogen atom.

[1-8] In the compound of Formula (I) according to Aspect [1], X is an oxygen atom, a sulfur atom, or $—NR^7—$ (R^7 is the same as defined as R^7 above).

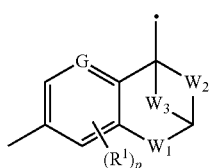
[1-8-a] Preferably, X is an oxygen atom or $—NH—$.

[1-8-b] More preferably, X is an oxygen atom.

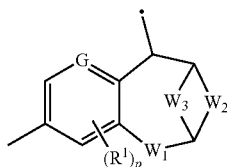
[1-9] In the compound of Formula (I) according to Aspect [1], j is an integer of 0 to 3, while k is an integer of 0 to 2. Preferably, j is 0 or 1, while k is 0. When the ring A is a monocyclic ring or a spiro ring, more preferably, j is 1, while k is 0.

When the ring A is a fused ring, more preferably, j is 0, while k is 0.

[1-10] In the compound of Formula (I) according to Aspect [1], the ring B is a C_{6-14} aryl group or a 5- to 14-membered heteroaryl group, preferably a benzene ring, a pyridine ring, a pyrimidine ring, or Formula (BB1) or Formula (BB2):



(BB1)



(BB2)

(where p and R^1 are the same as defined in Formula (I); G is a carbon atom or a nitrogen atom; W_1 is a single bond, an oxygen atom, a sulfur atom, $—CH_2—$, $—CF_2—$, $—CO—$, $—SO—$, or $—SO_2—$; W_2 is a single bond or $—CH_2—$; W_3 is none or $—CH_2—$; and \bullet is a single bond with a cyclic amide structure moiety). The ring B is more preferably a benzene ring, a pyridine ring, Formula (BB 1), or Formula (BB2), further preferably a benzene ring.

Preferable aspects of p and R^1 in Formula (BB1) and Formula (BB2) are the same as the preferable aspects described in the below Aspect [1-11] and the above Aspects [1-2-a] to [1-2-b].

[1-10-a] In Formula (BB1) or Formula (BB2), G is preferably a carbon atom.

[1-10-b] In Formula (BB1), W_1 is preferably an oxygen atom, a sulfur atom, or $—CH_2—$. When W_3 is $—CH_2—$, W_2 is preferably $—CH_2—$.

[1-10-c] In Formula (BB2), W_1 is preferably a single bond, an oxygen atom, a sulfur atom, or $—CH_2—$. When W_3 is $—CH_2—$, W_2 is preferably $—CH_2—$.

[1-11] In the compound of Formula (I) according to Aspect [1], p is an integer of 0 to 4. p is preferably 0 or 1.

[1-12] In the compound of Formula (I) according to Aspect [1], n is an integer of 0 to 2; h is an integer of 0 to 3; J_1 is

$—CR^{11a}R^{11b}—$ or $—NR^{11c}—$; and J_2 is $—CR^{12a}R^{12b}—$ or (with the proviso that when J_1 is $—NR^{11c}—$, h is 0). n is preferably 1 or 2. When

J_1 is $—CR^{11a}R^{11b}—$ and h is 0, n is more preferably 1.

5 When J_1 is $—NR^{11c}—$ and h is 0, n is more preferably 2.

When h is an integer of 1 to 3, n is more preferably 2.

[1-13] In the compound of Formula (I) according to Aspect [1], the ring A is a C_{6-14} aryl group which is optionally substituted with 1 to 5 L(s), a 3- to 14-membered heterocyclic group which is optionally substituted with 1 to 5 L(s), a C_{5-7} cycloalkyl group which is optionally substituted with 1 to 5 L(s), a C_{5-7} cycloalkenyl group which is optionally substituted with 1 to 5 L(s), a 6- to 14-membered spiro ring group which is optionally substituted with 1 to 5 L(s), or a 2-phenylamino-2-oxoacetyl group which is optionally substituted with 1 to 5 L(s).

[1-13-a] Preferably, the ring A is phenyl which is optionally substituted with 1 to 5 L(s), a C_{6-14} fused aryl group which is optionally substituted with 1 to 5 L(s) and partly hydrogenated, a 5- to 7-membered monocyclic heteroaryl group which is optionally substituted with 1 to 5 L(s), an 8- to 14-membered ring-fused heteroaryl group which is optionally substituted with 1 to 5 L(s), an 8- to 14-membered ring-fused heteroaryl group which is optionally substituted with 1 to 5 L(s) and partly hydrogenated, a 3- to 8-membered non-aromatic heterocyclic group which is optionally substituted with 1 to 5 L(s), a C_{5-7} cycloalkenyl group which is optionally substituted with 1 to 5 L(s), or a 7- to 13-membered spiro ring group which is optionally substituted with 1 to 5 L(s).

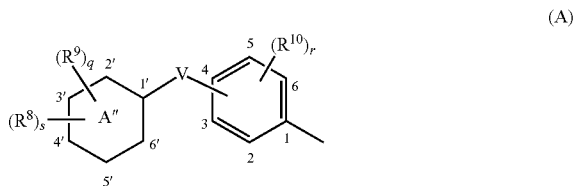
[1-13-b)] More preferably, the ring A is phenyl which is optionally substituted with 1 to 5 L(s), indanyl which is optionally substituted with 1 to 5 L(s), 1,2,3,4-tetrahydronaphthyl which is optionally substituted with 1 to 5 L(s), thienyl which is optionally substituted with 1 to 5 L(s), thiazolyl which is optionally substituted with 1 to 5 L(s), phthalazinyl which is optionally substituted with 1 to 5 L(s), 1,2,3,4-tetrahydro-4-isoquinolyl which is optionally substituted with 1 to 5 L(s), 1,2,3,4-tetrahydro-4-quinolyl which is optionally substituted with 1 to 5 L(s), dihydrobenzofuranyl which is optionally substituted with 1 to 5 L(s), chromanyl which is optionally substituted with 1 to 5 L(s), pyrrolidinyl which is optionally substituted with 1 to 5 L(s), piperidinyl which is optionally substituted with 1 to 5 L(s), a cyclohexenyl group which is optionally substituted with 1 to 5 L(s), or a 7- to 13-membered spiro ring group which is optionally substituted with 1 to 5 L(s).

[1-13-b-1] Further preferably, the ring A is phenyl which is optionally substituted with 1 to 5 L(s), thienyl which is optionally substituted with 1 to 5 L(s), thiazolyl which is optionally substituted with 1 to 5 L(s), phthalazinyl which is optionally substituted with 1 to 5 L(s), 1,2,3,4-tetrahydro-4-isoquinolyl which is optionally substituted with 1 to 5 L(s), 1,2,3,4-tetrahydro-4-quinolyl which is optionally substituted with 1 to 5 L(s), pyrrolidinyl which is optionally substituted with 1 to 5 L(s), piperidinyl which is optionally substituted with 1 to 5 L(s), a cyclohexenyl group which is optionally substituted with 1 to 5 L(s), or a 7- to 13-membered spiro ring group which is optionally substituted with 1 to 5 L(s).

[1-13-b-2] Most preferably, the ring A is phenyl which is optionally substituted with 1 to 5 L(s), thienyl which is optionally substituted with 1 to 5 L(s), thiazolyl which is optionally substituted with 1 to 5 L(s), pyrrolidinyl which is optionally substituted with 1 to 5 L(s), piperidinyl which is optionally substituted with 1 to 5 L(s), a cyclohexenyl group which is optionally substituted with 1 to 5 L(s), or a 7- to 13-membered spiro ring group which is optionally substituted with 1 to 5 L(s).

49

[1-13-c] The ring A in Formula (I) according to Aspect [1] is preferably phenyl that is optionally substituted with 1 to 5 L(s). More preferable examples of the ring A include Partial Structural Formula (A):



(where q and r are independently an integer of 0 to 4; s is an integer of 0 to 2 (with the proviso that q+s is an integer of 0 to 5);

the ring A' is an aryl group or a heteroaryl group;

V is a single bond or an oxygen atom;

R⁸s are independently a group optionally selected from a C₁₋₆ alkoxy group which is substituted with 1 to 5 substituent(s) M, a C₂₋₆ alkenyloxy group that is substituted with 1 to 5 substituent(s) M, a C₂₋₆ alkynyloxy group that is substituted with 1 to 5 substituent(s) M, a —CONR^dR^e group, an aralkyloxy group, a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)), and a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C₁₋₆ alkyl group(s) or 1 to 3 oxo group(s)); R⁸s are independently preferably a group optionally selected from a C₁₋₆ alkoxy group that is substituted with 1 to 5 substituent(s) M, a —CONR^dR^{e1} group, and an aralkyloxy group; R⁸s are independently more preferably a C₁₋₆ alkoxy group that is substituted with 1 to 5 substituent(s) M;

the substituents M are independently a group optionally selected from a halogen atom, —OH, a C₁₋₆ alkoxy group, an aryl group (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 —OH, 1 to 3 C₁₋₆ alkyl group(s), or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^{b1}R^{c1} group, a —SO₂NR^dR^e group, and a —CONR^dR^e group; the substituents M are independently preferably a group optionally selected from a halogen atom, —OH, a C₁₋₆ alkoxy group, a —S(O)_iR^a (i is an integer of 0 to 2 and R^a is a C₁₋₆ alkyl group or a halogenated C₁₋₆ alkyl group) group, a —NR^{b1}R^{c1} group, a —SO₂NR^dR^e group, and a —CONR^dR^e group; the substituents M are independently more preferably a group optionally selected from —OH, a C₁₋₆ alkoxy group, a —S(O)_iR^a (i is an integer of 0 to 2 and R^a is a C₁₋₆ alkyl group or a halogenated C₁₋₆ alkyl group) group, and a —NR^{b1}R^{c1} group;

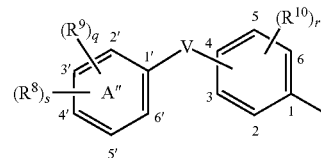
R⁹s and R¹⁰s are independently a group optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkenyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkynyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₆ alkoxy group that is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₇ alkanoyl group, —SH, a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^{b1}R^{c1} group, and a —CONR^dR^e group;

50

R⁹s are independently preferably a group optionally selected from a halogen atom, —OH, a cyano group, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2 and R^a is a C₁₋₆ alkyl group or a halogenated C₁₋₆ alkyl group) group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₆ alkenyl group, a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)), a C₂₋₇ alkanoyl group, a —S(O)_iR^a (i is an integer of 0 to 2 and R^a is a C₁₋₆ alkyl group or a halogenated C₁₋₆ alkyl group) group, a —NR^{b1}R^{c1} group, and a —CONR^dR^e group; R⁹s are independently more preferably a group optionally selected from a halogen atom, a cyano group, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), and a C₁₋₆ alkoxy group; the figures of 1 to 6 or 1' to 6' indicate where the ring A'-V— or each substituent is bonded; and R^a, R^d, R^e, R^{b1}, R^{c1}, and R^{e1} are the same as defined in Formula (I).

In Formula (A), the binding positions of the ring A'-V— and RN are any positions at which they can be optionally bonded in the benzene ring, and the binding positions of R⁸s and R⁹s are any positions at which they can be optionally bonded in the ring A'. In Formula (A), preferably, the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring. Namely, preferable examples of Formula (A) include Formula (A)-1:

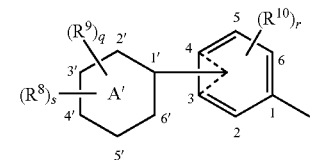
(A)-1



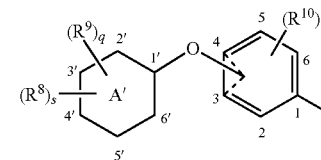
(where q, r, s, V, R⁸s, R⁹s, and R¹⁰s are the same as defined in Formula (A); and the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring).

[1-13-c-1] Preferable examples of Formula (A) include Formula (A1) or Formula (A2):

(A1)



(A2)



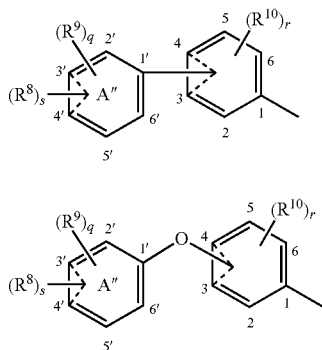
(where q, r, s, the ring A', R⁸s, R⁹s, and R¹⁰s are the same as defined in Formula (A) described in Aspect [1-13-c]; and the broken lines and the FIGS. 3 and 4 or the FIGS. 3' and 4' indicate where the ring A', the ring A'-O—, or R⁸s are bonded).

51

Here, when the position of the single bond of the phenyl group (the binding position with the linker moiety containing X) is determined as 1-position, the binding position of the ring A' in Formula (A1) is 3-position or 4-position, preferably 3-position. In the case that the ring A' is a 6-membered ring, when the binding position with the phenyl group of the ring A' is determined as 1'-position, the binding position of R⁸ in Formula (A1) is preferably 3'-position or 4'-position.

When the position of the single bond of the phenyl group (the binding position with the linker moiety containing X) is determined as 1-position, the binding position of the ring A'-O— in Formula (A2) is 3-position or 4-position, preferably 3-position. In the case that the ring A' is a 6-membered ring, when the binding position with the phenyl group-O— of the ring A' is determined as 1'-position, the binding position of R⁸ in Formula (A2) is preferably 3'-position or 4'-position.

In Formula (A1) or Formula (A2), preferably, the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring. Namely, preferable examples of Formula (A1) or Formula (A2) include Formula (A1)-1 or Formula (A2)-1:



(where q, r, s, R⁸, R⁹s, and R¹⁰s are the same as defined in Formula (A) described in Aspect [1-13-c]; the ring A'' is the same as defined in Formula (A)-1 described in Aspect [1-13-c]; and the broken lines and the FIGS. 3 and 4 or the FIGS. 3' and 4' indicate where the ring A'', the ring A''-O—, or R⁸s are bonded).

Here, when the position of the single bond of the phenyl group (the binding position with the linker moiety containing X) is determined as 1-position, the binding position of the ring A'' or the ring A''-O— in Formula (A1)-1 or Formula (A2)-1 is preferably 3-position. When the binding position with the phenyl group or the phenyl group-O— of the ring A'' is determined as 1'-position, the binding position of R⁸ in Formula (A1)-1 or Formula (A2)-1 is preferably 4'-position.

[1-13-c-1-1] More specifically, Formula (A) is preferably the above Partial Structural Formula (A1) or Formula (A1)-1.

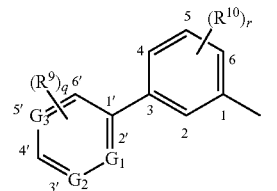
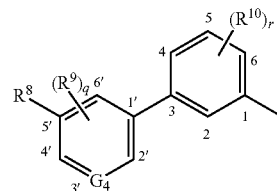
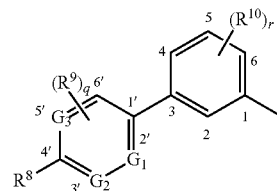
[1-13-c-2] In Formula (A), Formula (A1), or Formula (A2), more specifically, the ring A' is preferably benzene, naphthalene, pyridine, pyrimidine, thiophene, quinoline, benzimidazole, or dibenzofuran, more preferably benzene, pyridine, pyrimidine, thiophene, or quinoline. Further preferably, the ring A' is benzene, pyridine, or pyrimidine, that is, the ring A'' (Formula (A)-1, Formula (A1)-1, or Formula (A2)-1). Most preferably, the ring A' and the ring A'' are benzene or pyridine.

[1-13-c-3] More specifically, Formula (A) is more preferably the above Partial Structural Formula (A), Formula (A)-1,

52

Formula (A1), Formula (A2), Formula (A1)-1, or Formula (A2)-1 in which s is 0 or 1. Preferably, any one of q and s is 1 or more.

[1-13-c-3-1] More preferably, Formula (A) is Formula (A1a) or Formula (A1b) when s is 1 in Formula (A1)-1, and Formula (A) is Formula (A1c) when s is 0 in Formula (A1)-1:



(where q, r, R⁸, R⁹ and R¹⁰ are the same as defined in the above Formula (A) described in Aspect [1-13-c]; and G₁, G₂, G₃, and G₄ are a =CH— group, a =CR⁹— group, or a nitrogen atom (with the proviso that when G₁ is a nitrogen atom, G₂ and G₃ are a =CH— group or a =CR⁹— group)).

In Formula (A1a), Formula (A1b), or Formula (A1c), when the position of the single bond of the phenyl group (the binding position with the linker moiety containing X) is determined as 1-position, R¹⁰ can be bonded at 2-position, 4-position, 5-position, or 6-position. The binding position of R⁹ is any positions at which it can be optionally bonded in the ring including G₁ or G₄.

Formula (A) is more preferably Formula (A1a) or Formula (A1c).

[1-13-c-3-2] In Formula (A1a), preferably, G₁ is a =CH— group or a =CR⁹— group; and G₂ and G₃ are independently a =CH— group, a =CR⁹— group, or a nitrogen atom. More preferably, G₁ and G₃ are independently a =CH— group or a =CR⁹— group; and G₂ is a =CH— group, a =CR⁹— group, or a nitrogen atom.

In Formula (A1c), preferably, G₁ is a =CH— group or a =CR⁹— group; and G₂ and G₃ are independently a =CH— group, a =CR⁹— group or a nitrogen atom. More preferably, G₁ and G₃ are independently a =CH— group or a =CR⁹— group; and G₂ is a =CH— group, a =CR⁹— group, or a nitrogen atom.

[1-13-c-4] More specifically, Formula (A) is preferably Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), or Formula (A1c) in which r is 0 or 1. When r is not 0, at least one of the binding positions of R¹⁰ is preferably 2-position, and when r is 1, the binding position of R¹⁰ is preferably 2-position.

[1-13-c-5] More specifically, Formula (A) is preferably Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), or Formula (A1c) in which q is an integer of 0 to 3, more preferably Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), or Formula (A1c) in which q is an integer of 1 to 3. Preferably, any one of q and s is 1 or more.

[1-13-c-5-1] In Formula (A1a), when the binding position of the ring containing G₁ with 3-position of the phenyl group is determined as 1'-position, the binding position of R⁹ when q is 1 is preferably 2'-position (with the proviso that the case where G₁ is a nitrogen atom is excluded) or 6'-position. The binding positions of R⁹s when q is 2 are preferably 2'-position and 6'-position, 2'-position and 5'-position, or 5'-position and 6'-position (with the proviso that the case where the binding position is a nitrogen atom is excluded), and more preferably, 2'-position and 6'-position or 2'-position and 5'-position. The binding positions of R⁹ when q is 3 are preferably 2'-position, 5'-position, and 6'-position (with the proviso that the case where the binding position is a nitrogen atom is excluded).

In Formula (A1c), when the binding position of the ring containing G₁ with 3-position of the phenyl group is determined as 1'-position, the binding position of R⁹ when q is 1 is preferably 2'-position (with the proviso that the case where G₁ is a nitrogen atom is excluded) or 6'-position. The binding positions of R⁹s when q is 2 are preferably 2'-position and 6'-position, 2'-position and 5'-position, 2'-position and 4'-position, 4'-position and 6'-position, or 5'-position and 6'-position (with the proviso that the case where the binding position is a nitrogen atom is excluded), and more preferably, 2'-position and 6'-position, 2'-position and 5'-position, or 2'-position and 4'-position. The binding positions of R⁹s when q is 3 are preferably 2'-position, 5'-position and 6'-position, or 2'-position, 4'-position and 6'-position, or 2'-position, 4'-position and 5'-position (with the proviso that the case where the binding position is a nitrogen atom is excluded).

[1-13-c-6] In Formula (A1a), r is preferably 0 or 1. When r is 1, the binding position of R¹⁰ is preferably 2-position. When G₁ is a =CH— group or a =CR⁹— group, G₂ is a =CH— group or a nitrogen atom, G₃ is a =CH— group, and q is 1 or 2, the binding position(s) of R⁹(s) is more preferably 2'-position and/or 6'-position.

In Formula (A1c), r is preferably 0 or 1. When r is 1, the binding position of R¹⁰ is preferably 2-position. When G₁ is a =CH— group or a =CR⁹— group, G₂ is a =CH— group or a nitrogen atom, G₃ is a =CH— group, and q is 1 or 2, the binding position(s) of R⁹(s) is more preferably 2'-position and/or 6'-position.

[1-13-c-7] In Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), or Formula (A1b), R⁸s are independently a C₁₋₆ alkoxy group which is substituted with 1 to 5 substituent(s) Ma, a C₂₋₆ alkenyloxy group which is substituted with 1 to 5 substituent(s) Ma, a C₂₋₆ alkynyloxy group which is substituted with 1 to 5 substituent(s) Ma, a —CONR^dR^{e2} group, an aralkyloxy group, a non-aromatic heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 2 oxo group(s)), or a non-aromatic heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 2 oxo group(s)); the substituents Ma are independently a halogen atom, —OH, a C₁₋₆ alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 —OH, 1 to 3 C₁₋₆ alkyl group(s), or 1 to 3 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^{b1}R^{c1} group, a —SO₂NR^dR^e group, and a —CONR^dR^e group; and R^{e2} is a C₁₋₆ alkyl group (the

C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, 1 to 5 C₁₋₆ alkoxy group(s), 1 to 5 non-aromatic heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 —OH, 1 to 3 C₁₋₆ alkyl group(s), or 1 to 3 oxo group(s)), 1 to 5 —S(O)_iR^a (i is an integer of 0 to 2) group(s), 1 to 5 —SO₂NR^dR^e group(s), 1 to 5 —CONR^dR^e group(s), or 1 to 5 —NR^{b1}R^{c1} group(s)).

[1-13-c-7-1] More preferable examples of R⁸ include a C₁₋₆ alkoxy group (the alkoxy group is substituted with 1 to 5 group(s) optionally selected from —OH, a C₁₋₆ alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 —OH, 1 to 2 C₁₋₄ alkyl group(s), or 1 to 2 oxo group(s)), a —S(O)_iR^a (i is an integer of 0 to 2) group, a —NR^{b2}R^{c2} group, a —SO₂NR^dR^e group, and a —CONR^dR^e group), a —CONR^{d3}R^{e3} group, an aralkyloxy group, a non-aromatic heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 2 oxo group(s)), and a non-aromatic heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 2 oxo group(s)); R^{b2} and R^{c2} are independently a group optionally selected from a hydrogen atom, a C₁₋₆ alkyl group, a C₂₋₇ alkanoyl group (the alkanoyl group is optionally substituted with —OH or a C₁₋₆ alkoxy group), and a C₁₋₆ alkylsulfonyl group, where R^{b2} and R^{c2} optionally form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, and in the cyclic group, one carbon atom is optionally substituted with a carbonyl group; and R^{d3} is a hydrogen atom or a C₁₋₄ alkyl group, and R^{e2} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 group(s) optionally selected from —OH, a C₁₋₆ alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 —OH, 1 to 2 C₁₋₄ alkyl group(s), or 1 to 2 oxo group(s)), and a —S(O)_iR^a (i is an integer of 0 to 2)).

[1-13-c-7-2] Further preferable examples of R⁸ include a C₁₋₆ alkoxy group (the alkoxy group is substituted with 1 to 5 —OH, 1 to 5 methoxy, 1 to 5 ethoxy, 1 to 5 4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 1 to 5 3-methyloxetane-3-yl, 1 to 5 methylsulfonyl, 1 to 5 ethylsulfonyl, 1 to 5 —NH₂, 1 to 5 acetamino, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, 1 to 5 5-oxo-2-pyrrolidinyl, 1 to 5 sulfamoyl, 1 to 5 methylsulfamoyl, 1 to 5 dimethylsulfamoyl, 1 to 5 carbamoyl, 1 to 5 methylcarbamoyl, or 1 to 5 dimethylcarbamoyl), a —CONR^{d4}R^{e4} group (R^{d4} is a hydrogen atom or a C₁₋₄ alkyl group; and R^{e4} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 —OH, 1 to 5 methoxy, 1 to 5 ethoxy, 1 to 5 4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 1 to 5 3-methyloxetane-3-yl, 1 to 5 methylsulfonyl, 1 to 5 ethylsulfonyl, 1 to 5 —NH₂, 1 to 5 acetamino, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, 1 to 5 5-oxo-2-pyrrolidinyl, 1 to 5 sulfamoyl, 1 to 5 methylsulfamoyl, 1 to 5 dimethylsulfamoyl, 1 to 5 carbamoyl, 1 to 5 methylcarbamoyl, or 1 to 5 dimethylcarbamoyl), benzyloxy, (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy, and (pyrrolidine-1-yl)carbonyl. The substitution number of —OH, methoxy, ethoxy, 4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 3-methyloxetane-3-yl, methylsulfonyl, ethylsulfonyl, —NH₂, acetamino, methylsulfonylamino, 2-oxo-1-pyrrolidinyl, 5-oxo-2-pyrrolidinyl, sulfamoyl, methylsulfamoyl, dimethylsulfamoyl, carbamoyl, methylcarbamoyl, or dimethylcarbamoyl in the C₁₋₆ alkoxy group as R⁸ or the C₁₋₆ alkyl group as R^{e4} is particularly preferably 1 to 2.

More specifically, R⁸ is 2-hydroxyethoxy, 3-hydroxypropoxy, 3-hydroxybutoxy, 3-hydroxy-3-methylbutoxy, 2,3-dihydroxypropoxy, (2R)-2,3-dihydroxypropoxy, (2S)-2,3-dihydroxypropoxy, (3S)-3-hydroxybutoxy, (3R)-3-

55

hydroxybutoxy, 3-hydroxy-2-hydroxymethylpropoxy, 3-hydroxy-2-hydroxymethyl-2-methylpropoxy, 2-ethoxy-ethoxy, (4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methoxy, (3-methyloxetane-3-yl)methoxy, 2-methylsulfonyl-ethoxy, 3-methylsulfonyl-propoxy, 2-ethylsulfonyl-ethoxy, 3-ethylsulfonyl-propoxy, 2-aminoethoxy, 3-aminopropoxy, 2-acetyl-amino-ethoxy, 3-acetyl-amino-propoxy, 2-methylsulfonylamino-ethoxy, 3-methylsulfonylamino-propoxy, 2-(2-oxo-1-pyrrolidinyl)ethoxy, 3-(2-oxo-1-pyrrolidinyl)propoxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-sulfamoyl-ethoxy, 3-sulfamoyl-propoxy, 2-methylsulfamoyl-ethoxy, 3-methylsulfamoyl-propoxy, 2-dimethylsulfamoyl-ethoxy, 3-dimethylsulfamoyl-propoxy, 2-carbamoyl-ethoxy, 3-carbamoyl-propoxy, 2-methylcarbamoyl-ethoxy, 3-methylcarbamoyl-propoxy, 2-dimethylcarbamoyl-ethoxy, 3-dimethylcarbamoyl-propoxy, N-(2-hydroxyethyl)carbamoyl, N-(2-methoxyethyl)carbamoyl, N-(2-hydroxyethyl)-N-methylcarbamoyl, N-(2-methoxyethyl)-N-methylcarbamoyl, N-(2-methylsulfonyl-ethyl)carbamoyl, N-(2-methylsulfonyl-ethyl)-N-methylcarbamoyl, (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy, benzyloxy, (pyrrolidine-1-yl)carbonyl, or the like.

The C_{1-6} alkoxy group or the heterocyclic oxy group which are substituted with a group of A in Formula (I) or the like in WO 2010/143733 pamphlet, particularly the C_{1-6} alkoxy groups substituted with (2) to (8) which are shown in [9] (c) in pp. 25 and 26 or the heterocyclic oxy group shown in [9] (e), and these groups shown in Examples can also be referred to as specific examples of R^8 of the present specification. Similarly, formulae and the corresponding groups shown in Examples in the pamphlets below can also be referred to as specific examples of R^8 of the present specification. WO 2008/001931 pamphlet, a group of R^1-X-O- in Formula (I);

WO 2010/123017 pamphlet, a group of R^7 in Formula (I); WO 2010/123016 pamphlet, a group of R^{10} in Formula (I); WO 2009/054423 pamphlet, groups of A and B in Formula (II).

[1-13-c-8] In Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), or Formula (A1c), preferable examples of R^9 s independently include a halogen atom, a cyano group, a C_{1-4} alkyl group (the C_{1-4} alkyl group is optionally substituted with 1 to 5 halogen atom(s) or 1 to 5 —OH), a C_{2-4} alkenyl group, a C_{1-4} alkoxy group (the C_{1-4} alkoxy group is optionally substituted with 1 to 5 halogen atom(s)), a C_{2-5} alkanoyl group, a —S(O) R^a (R^a is a C_{1-4} alkyl group) group, a —CONR d R e (R^d and R^e are independently a hydrogen atom or a C_{1-4} alkyl group) group, and a —NR b1 R c1 group (R^{b1} and R^{c1} form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group; and in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom or with a carbonyl group).

More preferably, R^9 s are independently a halogen atom, a cyano group, a C_{1-4} alkyl group (the C_{1-4} alkyl group is optionally substituted with 1 to 5 halogen atom(s) or 1 to 5 —OH), a C_{2-3} alkenyl group, a C_{1-4} alkoxy group (the C_{1-4} alkoxy group is optionally substituted with 1 to 5 halogen atom(s)), a C_{2-3} alkanoyl group, a —S(O) R^a (R^a is a C_{1-2} alkyl group) group, a —CONR d R e (R^d and R^e are independently a hydrogen atom or a C_{1-2} alkyl group) group, or a —NR b1 R c1 group (R^{b1} and R^{c1} form, together with a nitrogen atom to which they are bonded, a 3- to 6-membered cyclic group; and in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an oxygen atom, a nitrogen

56

atom, or a carbonyl group). Further preferably, R^9 s are independently a halogen atom, a cyano group, a C_{1-4} alkyl group which is optionally substituted with 1 to 5 halogen atom(s), or a C_{1-4} alkoxy group which is optionally substituted with 1 to 5 halogen atom(s).

More specific examples of R^9 include a fluorine atom, a chlorine atom, a bromine atom, cyano, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, cyclopropylmethoxy, trifluoromethoxy, trifluoroethoxy, vinyl, acetyl, methylsulfonyl, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1-piperidinyl, 4-morpholinyl, and 2-oxooxazolidin-3-yl. More preferable examples of R^9 include a fluorine atom, cyano, methyl, ethyl, methoxy, and ethoxy.

The amino group, the C_{1-6} alkylthio group, the C_{1-6} alkyl group, the C_{3-10} cycloalkyl group, or the C_{1-6} alkoxy group which are substituted with a group of A in Formula (I) or the like in WO 2010/143733 pamphlet, particularly the C_{1-6} alkyl group and the halogenated C_{1-6} alkyl group which are shown in [9] (b) in pp. 25 and 26 or the C_{1-6} alkoxy group which is optionally substituted with (1) shown in [9] (c), and the corresponding groups shown in Examples can also be referred to as specific examples of R^9 of the present specification. Similarly, formulae and the corresponding groups shown in Examples in the pamphlets below can also be referred to as specific examples of R^9 of the present specification.

WO 2008/001931 pamphlet, groups of R^2 , R^3 , R^4 , and R^5 in Formula (I);

WO 2010/123017 pamphlet, groups of R^5 , R^6 , R^7 , and R^7 in Formula (I);

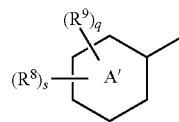
WO 2010/123016 pamphlet, groups of R^8 , R^9 , R^{10} , and R^7 in Formula (I);

WO 2009/054423 pamphlet, groups of R^3 , R^4 , A, and B in Formula (II) and Formula (III).

[1-13-c-9] In Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), or Formula (A1c), preferable examples of R^{10} s independently include a halogen atom, a C_{1-4} alkyl group which is optionally substituted with 1 to 5 halogen atom(s), and a C_{1-4} alkoxy group which is optionally substituted with 1 to 5 halogen atom(s). More specific examples of R^{10} include a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, and trifluoromethoxy. More preferable examples of R^{10} include a fluorine atom, methyl, ethyl, methoxy, and ethoxy.

[1-13-c-10] The preferable aspects of q, s, the ring A', R^8 , and R^9 of the Partial Structural Formula (A'):

(A')



(where q, s, the ring A', R^8 , and R^9 are the same as defined in Formula (A) in Aspect [1-13-c]) in Formula (A), Formula (A1), and Formula (A2) are the same as the preferable aspects described in Aspects [1-13-c-2], [1-13-c-3], [1-13-c-5], [1-13-c-7], [1-13-c-7-1], [1-13-c-7-2], or [1-13-c-8]. Examples of the preferable aspect of Formula (A') include the same groups as the groups having an aryl group or a het-

eroaryl group among the preferable aspects of I described in Aspect [1-1-d]. Specific examples of Formula (A') include specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" or the same groups as the groups having a heteroaryl group among specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" that are described in Aspect [1]. More specific examples of Formula (A') include the same groups as the groups having benzene, naphthalene, pyridine, pyrimidine, thiophene, quinoline, benzimidazole, or dibenzofuran.

Specific examples of the ring A' moiety having (R⁸)_q and (R⁹)_q in Formula (A)-1, Formula (A1)-1, and Formula (A2)-1 include the same groups as the groups having a benzene ring, a pyridine ring, or a pyrimidine ring among specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" and specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" that are described in Aspect [1].

Specific examples of the ring moiety having R⁸ and (R⁹)_q in Formula (A1a), Formula (A1b), and Formula (A1c) include the groups having a benzene ring, a pyridine ring, or a pyrimidine ring and having any group of R⁸ at the p-position or the m-position or not having any group of R⁸ among specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" and specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" that are described in Aspect [1]. For example in Formula (A1a), specific examples of the ring moiety having R⁸ and (R⁹)_q include a phenyl group having any group of R⁸ at 4-position (such as 4-(3-hydroxy-3-methylbutoxy)phenyl) and a 3-pyridinyl group having any group of R⁸ at 6-position (such as 6-(3-methylsulfonyl-propoxy)pyridin-3-yl) and further include also a group having simultaneously any groups of R⁹ (such as 4-(2-ethoxy-ethoxy)-2,6-dimethylphenyl and 6-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-2-methylpyridin-3-yl).

Specific examples of the ring A' moiety having (R⁸)_q and (R⁹)_q of the present specification also include the groups of A in Formula (I) or the like in WO 2010/143733 pamphlet and the groups of Q in Formula (V) in WO 2007/033002 pamphlet, particularly the groups having a cyclic group among the corresponding groups shown in Examples of these pamphlets. Similarly, also the corresponding groups shown in formulae and Examples in the pamphlets below can be referred to as the specific examples of the ring A' moiety having (R⁸)_q and (R⁹)_q of the present specification.

WO 2008/001931 pamphlet, phenyl groups having R¹—X—O—, R², R³, R⁴, and R⁵ in Formula (I);

WO 2010/123017 pamphlet, 6-membered cyclic groups having R⁵, R⁶, and R⁷ in Formula (I);

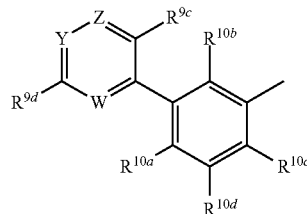
WO 2010/123016 pamphlet, 6-membered cyclic groups having R⁸, R⁹, and R¹⁰ in Formula (I);

WO 2009/054423 pamphlet, groups of Formula (II) and Formula (III).

That is, 4-(3-methylsulfonyl-propoxy)-2,6-dimethylphenyl, 4-((1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy)-2,6-dimethylphenyl, 2-(4-morpholino)-4,6-dimethylpyrimidin-5-yl, 2-ethyl-6,7-difluoro-1H-benzimidazol-1-yl, 2-ethoxy-6,7-difluoro-1H-benzimidazol-1-yl, and the like are mentioned.

[1-13-c-11] Preferable examples of the ring A in Formula (I), Formula (A), Formula (A)-1, Formula (A1), Formula (A1)-1, or Formula (A1c) include Formula (A1)-1-1:

(A1)-1-1



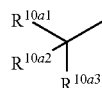
(where W, Y, and Z are —CH— or a nitrogen atom (with the proviso that 0 or 1 of W, Y, and Z is a nitrogen atom, and when R^{9c} is a fluorine atom, Z is —CH—);

R^{9c} is a hydrogen atom, a fluorine atom, a chlorine atom, a trifluoromethyl group, or a C₁₋₆ alkoxy group; R^{9d} is a hydrogen atom, a fluorine atom, a chlorine atom, —OH, a C₁₋₄ alkyl group, a C₁₋₃ alkoxy group, or a C₁₋₂ alkylthio group;

R^{10a} is a C₁₋₁₀ alkyl group (the C₁₋₁₀ alkyl group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₄ alkoxy group (the C₁₋₄ alkoxy group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₂ alkoxy group)), a C₂₋₁₀ alkenyl group (the C₂₋₁₀ alkenyl group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₄ alkoxy group(s) (the C₁₋₄ alkoxy group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₂ alkoxy group(s))), a C₁₋₁₀ alkoxy group (the C₁₋₁₀ alkoxy group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₂ alkoxy group(s)), or a C₂₋₁₀ alkenyloxy group (the C₂₋₁₀ alkenyloxy group is optionally substituted with 1 to 4 halogen atom(s), 1 to 4 —OH, or 1 to 4 C₁₋₂ alkoxy group(s)); and

R^{10b}, R^{10c}, and R^{10d} are independently a hydrogen atom, a fluorine atom, a chlorine atom, a C₁₋₄ alkyl group, or a C₁₋₄ alkoxy group).

In Formula (A1)-1-1, preferable examples of R^{10a} include Formula (R^{10a}):

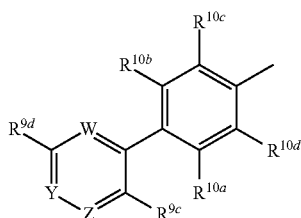
(R^{10a})

(where R^{10a1}, R^{10a2}, and R^{10a3} are independently a hydrogen atom, a fluorine atom, or a C₁₋₄ alkyl group; at least two of R^{10a1}, R^{10a2}, and R^{10a3} are other than a hydrogen atom; and R^{10a1}, R^{10a2}, and R^{10a3} optionally form, together with a carbon atom to which they are bonded, a 3- to 8-membered cyclic group). Preferably, all of R^{10a1}, R^{10a2}, and R^{10a3} are a methyl group, or R^{10a1}, R^{10a2}, and R^{10a3} form a cyclopropyl group. In Formula (A1)-1-1, W, Y, and Z are preferably —CH—, R^{9c} is preferably a fluorine atom or a butoxy group, R^{9d} is preferably a methoxy group, and R^{10b}, R^{10c}, and R^{10d} are preferably a hydrogen atom.

Specific examples of Formula (A1)-1-1 include 6-(1,1-dimethylethyl)-2'-fluoro-5'-methoxy-1,1'-biphenyl-3-yl and 2'-butoxy-6-(1,1-dimethylethyl)-5'-methoxy-1,1'-biphenyl-3-yl.

[1-13-c-12] Preferable examples of the ring A in Formula (I), Formula (A), Formula (A)-1, Formula (A1), or Formula (A1)-1 include Formula (A1)-1-2:

59

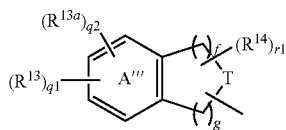


(where W, Y, Z, R^{9c} , R^{1d} , R^{10a} , R^{10b} , R^{10c} , and R^{10d} are the same as defined in Formula (A1)-1-1 described in Aspect [1-13-c-11]).

In Formula (A1)-1-2, an alkyl chain or an alkenyl chain of R^{10a} is a linear, branched, or cyclic chain and also includes a linear chain or branched chain group substituted with a cyclic group and a cyclic group substituted with a linear chain or branched chain group. When R^{10a} is a C_{1-10} alkyl group, specific examples of R^{10a} include Formula (R^{10a}) described in Aspect [1-13-c-11]. More specific examples of R^{10a} include 1,1-dimethylethyl(tert-butyl), 2,2-dimethylcyclopentyl, 5,5-dimethylcyclopent-1-enyl, 2,2-dimethyl-1-hydroxypropyl, and 2,2-dimethyl-1-methoxypropyl. Specific examples of R^{10a} of the present specification also include a group of A in Formula I in WO 2009/048527 pamphlet, a group of A in Formula I and Formula III in WO 2009/111056 pamphlet, and a group of A in Formula I'A in WO 2010/045258 pamphlet, particularly the corresponding groups shown in Examples.

In Formula (A1)-1-2, W and Z are preferably $-\text{CH}-$, R^{9c} is preferably a fluorine atom, R^{9d} is preferably a methoxy group, R^{10b} and R^{10d} are preferably a hydrogen atom, and R^{10c} is preferably a hydrogen atom or a fluorine atom. Specific examples of Formula (A1)-1-2 include 2-(1,1-dimethylethyl)-2'-fluoro-5'-methoxy-1,1'-biphenyl-4-yl, 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-1,1'-biphenyl-4-yl, and 2-(2,2-dimethyl-1-methoxypropyl)-2'-fluoro-5'-methoxy-1,1'-biphenyl-4-yl.

[1-13-d] The ring A in Formula (I) according to Aspect [I] is preferably Partial Structural Formula (AA):



(where f is an integer of 0 to 2; g is an integer of 1 to 4; q1 is an integer of 0 to 3; q2 is 0 or 1; r1 is an integer of 0 to 2 (with the proviso that $q1+q2+r1$ is an integer of 0 to 5); the ring A''' is a benzene ring or a pyridine ring;

T is $-\text{CH}_2-$, an oxygen atom, $-\text{S(O)}_i-$ (i is an integer of 0 to 2), or $-\text{NR}^7-$ (R^7 is the same as R^7 defined in Formula (I));

R^{13} s are independently a group optionally selected from a halogen atom, $-\text{OH}$, a cyano group, a C_{1-10} alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{1-10} alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10}

60

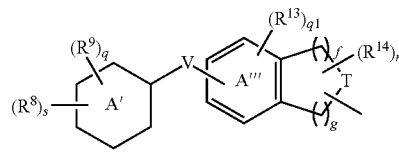
alkynyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, $-\text{SH}$, a $-\text{S(O)}_i\text{R}^a$ (i is an integer of 0 to 2) group, and a $-\text{NR}^b\text{R}^c$ group;

R^{13a} is a group optionally selected from an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, and a substituted spiroperidinylmethyl group;

R^{14} s are independently a group optionally selected from a halogen atom, $-\text{OH}$, a cyano group, a C_{1-6} alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C_{1-6} alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, $-\text{SH}$, a $-\text{S(O)}_i\text{R}^a$ (i is an integer of 0 to 2) group, and a $-\text{NR}^b\text{R}^c$ group; and

R^a , R^b , R^c , the substituent RI, and the substituent RII are the same as defined in Formula (I)). In Formula (AA), the binding positions of the linker moiety containing X and R^{14} s are any positions at which they can be optionally bonded in the ring containing T, and the binding positions of R^{13} and R^{13a} are any positions at which they can be optionally bonded in the ring A'''.

[1-13-d-1] Specific examples of Formula (AA) include Formula (AA)-1:

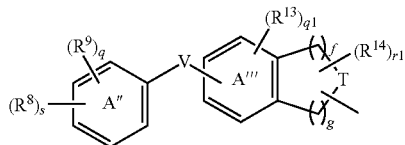


(where f, g, q1, r1, the ring A''', T, R^{13} , and R^{14} are the same as defined in Formula (AA) described in Aspect [1-13-d]; and q, s, the ring A', V, R^8 , and R^9 are the same as defined in Formula (A) described in Aspect [1-13-c]). In Formula (AA)-1, the binding positions of the linker moiety containing X and R^{14} s are any positions at which they can be optionally bonded in the ring containing T; the binding positions of the ring A'-V—and R^{13} are any positions at which they can be optionally bonded in the ring A'''; and the binding positions of R^8 and R^9 are any positions at which they can be optionally bonded in the ring A'.

The Formula (AA)-1 is preferably a Formula (AA)-1 in which the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring. That is, preferable examples of Formula (AA)-1 include Formula (AA)-1-1:

61

(AA)-1-1

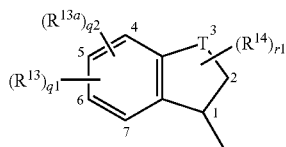


(where f, g, q1, r1, the ring A''', T, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; q, s, V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; and the ring A'' is the same as defined in Formula (A)-1 described in Aspect [1-13-c]).

[1-13-d-2] In Formula (AA), Formula (AA)-1, or Formula (AA)-1-1, the ring A''' is preferably a benzene ring.

[1-13-d-3] In Formula (AA), Formula (AA)-1, or Formula (AA)-1-1, f is preferably 0 or 1, more preferably 0. g is preferably 2 or 3, more preferably 2. Preferably, f is 0 and g is 2.

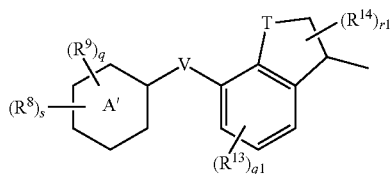
[1-13-d-4] Specific examples of Formula (AA) include Formula (AA1):



(where q1, q2, r1, T, R¹³, R^{13\alpha}, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and the FIGS. 1 to 7 indicate the binding position of a substituent in the ring).

[1-13-d-4-1] In Formula (AA1), when the binding position of the linker moiety containing X is determined as 1-position, the substitution position of R^{13\alpha} is preferably 4-position or 5-position, more preferably 4-position.

[1-13-d-5] More specifically, Formula (AA), Formula (AA)-1, Formula (AA)-1-1, or Formula (AA1) is preferably Formula (AA1)-1:

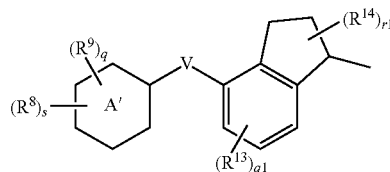


(where q1, r1, T, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and q, s, the ring A', V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]).

[1-13-d-5-1] Specific examples of Formula (AA1)-1 include Formula (AA1a)-1:

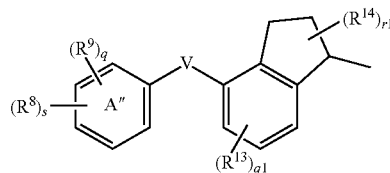
62

(AA1a)-1



(where q1, r1, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and q, s, the ring A', V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]).

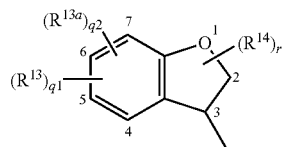
The Formula (AA1a)-1 is preferably a Formula (AA1a)-1 in which the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring. That is, preferable examples of Formula (AA1a)-1 include Formula (AA 1a)-1-1:



(where q1, r1, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; q, s, V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; and the ring A'' is the same as defined in Formula (A)-1 described in Aspect [1-13-c]).

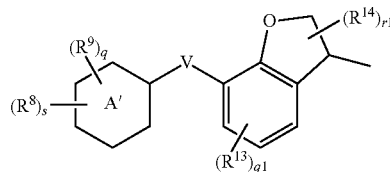
[1-13-d-6] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), or Formula (AA1)-1, T is preferably —CH₂— or an oxygen atom.

[1-13-d-7] More specific examples of Formula (AA) or Formula (AA1) include Formula (AA1b):



(where q1, q2, r1, R¹³, R^{13\alpha}, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and the FIGS. 1 to 7 indicate the binding position of a substituent in the ring).

[1-13-d-7-1] More specific examples of Formula (AA1)-1 or Formula (AA1b) include Formula (AA1b)-1:



(where q1, r1, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and q, s, the ring A', V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]).

[1-13-d-8] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1, q1 is preferably 0 or 1, more preferably 0.

[1-13-d-9] In Formula (AA), Formula (AA1), or Formula (AA1b), q2 is preferably 1.

[1-13-d-10] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1, r1 is preferably 0 or 1, more preferably 0.

[1-13-d-11] In Formula (AA), Formula (AA1), or Formula (AA1b), preferable examples of R^{13a} include a group optionally selected from an aryl group which is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII, and a substituted spiropiperidinylmethyl group (the substituent RII is the same as defined in Aspect [1]).

[1-13-d-11-1] In Formula (AA), Formula (AA1), or Formula (AA1b), more preferable examples of R^{13a} include a group optionally selected from an aryl group which is optionally substituted with 1 to 5 substituent(s) RIIa, a heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RIIa, an aralkyl group which is optionally substituted with 1 to 5 substituent(s) RIIa, a non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RIIa, an aryloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, a heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, a non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, an aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RIIa, and a substituted spiropiperidinylmethyl group (the substituent RIIa is the same as defined in Aspect [1-1-d]). The number of substitutions by the substituent RIIa is preferably 1 to 3.

[1-13-d-11-2] In Formula (AA), Formula (AA1), or Formula (AA1b), more specific examples of R^{13a} include the groups specifically exemplified as the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII", the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII", the "aralkyl group which is optionally substituted with 1 to 5 substituent(s) RII", the "heteroarylalkyl group which is optionally substituted with 1 to 5 substituent(s) RII", the "non-aromatic heterocyclic alkyl group which is optionally substituted with 1 to 5 substituent(s) RII", the "aryloxy group which is optionally substituted with 1 to 5 substituent(s) RII", the "heteroaryloxy group which is optionally substituted with 1 to 5 substituent(s) RII", the "non-aromatic heterocyclic oxy group which is optionally substituted with 1 to 5 substituent(s) RII", the "aralkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII", the "heteroarylalkyloxy group which is optionally substituted with 1 to 5 substituent(s) RII", the "substituted spiropiperidinylmethyl group", and the like.

Specific examples of R^{13a} of the present specification also include the groups of A in Formula (II) in WO 2010/143733 pamphlet and the groups of Q in Formula (V) in WO 2007/033002 pamphlet, particularly the groups having a cyclic group among the corresponding groups shown in Examples of these pamphlets.

[1-13-d-11-3] Specific examples of R^{13a} include, in addition to the Partial Structural Formula (A') described in Aspect [1-13-c-10], a group in which Formula (A') is substituted with an oxygen atom, a C₁₋₆ alkyl group, or a C₁₋₆ alkoxy group. Particularly, when R^{13a} is a group of Formula (A') or a group in which Formula (A') is substituted with an oxygen atom (Formula (A')—O—), R^{13a} can be Formula (A')—V—. For example, a Formula (AA) in which R^{13a} is Formula (A') can be a Formula (AA)-1 in which V is a single bond. A Formula (AA) in which R^{13a} is Formula (A')—O— can be a Formula (AA)-1 in which V is an oxygen atom.

In Formula (AA)-1, Formula (AA1)-1, Formula (AA1a)-1, or Formula (AA1b)-1, more specific examples of the Formula (A')—V— moiety when V is a single bond include the specific groups of the Partial Structural Formula (A') described in Aspect [1-13-c-10], that is, the same groups as specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII", or the groups having a heteroaryl group among specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" that are described in Aspect [1]. More specific examples of the Formula (A')—V— moiety when V is an oxygen atom include the groups in which the specific groups of the Partial Structural Formula (A') described in Aspect [1-13-c-10] are substituted with an oxygen atom, that is, the groups in which the same groups as specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII", or the groups having a heteroaryl group among specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII", are substituted with an oxygen atom.

[1-13-d-12] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1, preferable examples of R¹³ include a group optionally selected from a halogen atom, a cyano group, a C₁₋₆ alkyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkenyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkynyl group which is optionally substituted with 1 to 5 substituent(s) RI, a C₁₋₆ alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkenyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, a C₂₋₆ alkynyloxy group which is optionally substituted with 1 to 5 substituent(s) RI, and a —NR^bR^c group (the substituent RI is the same as defined in Aspect [1]).

[1-13-d-12-1] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1, more preferable examples of R¹³ include a group optionally selected from a halogen atom, a cyano group, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₂₋₆ alkenyl group (the C₂₋₆ alkenyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)), and a C₂₋₆ alkenyloxy group (the C₂₋₆ alkenyloxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 —OH, or 1 to 5 C₁₋₄ alkoxy group(s)).

65

[1-13-d-12-2] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1, specific examples of R^{13} include the groups specifically exemplified as the cyano group, the “halogen atom”, the “ C_{1-6} alkyl group which is optionally substituted with 1 to 5 substituent(s) RI”, the “ C_{1-6} alkoxy group which is optionally substituted with 1 to 5 substituent(s) RI”, and the like. More specific examples of R^{13} include a fluorine atom, a chlorine atom, a bromine atom, cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, and trifluoromethoxy.

[1-13-d-13] In Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or

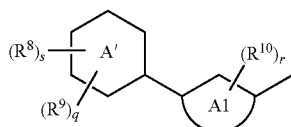
Formula (AA1b)-1, preferable examples of R^{14} include a halogen atom and a C_{1-4} alkyl group which is optionally substituted with 1 to 5 halogen atom(s). More specific examples of R^{14} include a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, and trifluoromethyl.

[1-13-d-14] In Formula (AA)-1, Formula (AA)-1-1, Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, or Formula (AA1b)-1, preferable aspects of the ring A', the ring A", R^8 , and R^9 are the same as the preferable aspects described in Aspects [1-13-c-2], [1-13-c-7], [1-13-c-7-1] [1-13-c-7-2], or [1-13-c-8]. The ring A' moiety having $(R^8)_s$ and $(R^9)_q$ can be Formula (A') described in Aspect [1-13-c-10] and the preferable aspects of the ring A' moiety having $(R^8)_s$ and $(R^9)_q$ are the same as the preferable aspects described in Aspect [1-13-c-10].

[1-13-d-15] In Formula (AA)-1, Formula (AA)-1-1, Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, or Formula (AA1b)-1, s is preferably 0 or 1. q is preferably an integer of 0 to 3, more preferably an integer of 0 to 2, further preferably 1 or 2. Preferably, any one of q and s is 1 or more.

[1-13-d-15-1] In Formula (AA)-1, Formula (AA)-1-1, Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, or Formula (AA1b)-1, when s is 1, the binding position of R^8 in the ring A' is preferably the m-position or the p-position, more preferably the p-position, relative to the binding position of V.

[1-13-e] Preferable examples of the ring A in Formula (I) include the Partial Structural Formula (A)-IV:



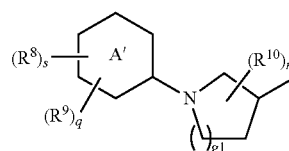
(where q, r, s, the ring A', R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and the ring A1 is a 5- or 6-membered heterocyclic group).

In Formula (A)-IV, the binding positions of R^{10} s are any positions at which they can be optionally bonded in the ring A1, and the binding positions of R^8 s and R^9 s are any positions at which they can be optionally bonded in the ring A'.

[1-13-e-1] In Formula (A)-IV, the ring A1 is a 5- or 6-membered non-aromatic heterocyclic group or a 5- or 6-membered heteroaryl group, and specifically, the ring A1 is preferably pyrrolidine, piperidine, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, isoxazole, 1,2,3-triazole, or 1,2,4-oxadiazole. More preferably, the ring A1 is pyrrolidine, piperidine, furan, thiophene, oxazole, or thiazole, further preferably pyrrolidine, piperidine, thiophene, or thiazole.

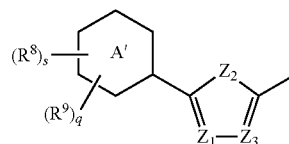
66

[1-13-e-2] The ring A in Formula (I), or Formula (A)-IV is preferably the Partial Structural Formula (A1)-IV:



(where q, r, s, the ring A', R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and g1 is 1 or 2). In Formula (A1)-IV, the binding positions of R^{10} s are any positions at which they can be optionally bonded in the pyrrolidine or piperidine ring, and the binding positions of R^8 s and R^9 s are any positions at which they can be optionally bonded in the ring A'.

[1-13-e-3] Preferable examples of the ring A in Formula (I), or Formula (A)-IV include the Partial Structural Formula (A2)-IV:



(where q, s, the ring A', R^8 , and R^9 are the same as defined in Formula (A) described in Aspect [1-13-c]; Z_1 is $—CR^{10e}—$ or a nitrogen atom; Z_2 is a sulfur atom or an oxygen atom; Z_3 is $—CR^{10f}—$ or a nitrogen atom; R^{10e} and R^{10f} are independently a hydrogen atom, a C_{1-6} alkyl group, or a methoxy group (with the proviso that at least one of Z_1 and Z_3 is $—CR^{10e}—$ or $—CR^{10f}—$)). In Formula (A2)-IV, the binding positions of R^8 s and R^9 s are any positions at which they can be optionally bonded in the ring A'. Here, in Formula (A2)-IV, the ring A' may be a substituted spiro piperidinylmethyl group in addition to the above description.

Specific examples of Formula (A2)-IV include Formula (A3)-IV described in Aspect [1-13-e-7] below and Formula (A4)-IV described in Aspect [1-13-e-8] below. Specific examples of Formula (A2)-IV of the present specification also include groups corresponding to Formula (A2)-IV of the present specification in WO 2005/086661 pamphlet, WO 2005/051890 pamphlet, WO 2004/022551 pamphlet, and WO 2004/011446 pamphlet (such as a 5-membered ring group and the like as examples of W in [0195] in p. 25 of WO 2005/086661 pamphlet), particularly the corresponding groups shown in Examples of these pamphlets.

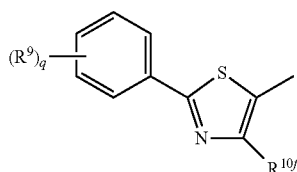
[1-13-e-4] In Formula (A)-IV, Formula (A1)-IV, or Formula (A2)-IV, more specifically, the ring A' is preferably benzene, pyridine, or pyrimidine. More preferably, the ring A' is benzene or pyridine, further preferably benzene.

[1-13-e-5] In Formula (A)-IV, Formula (A1)-IV, or Formula (A2)-IV, more specifically, s is preferably 0 or 1, and when s is 1 and the ring A' is a 6-membered ring, the substitution position of R^8 is preferably p-position. q is more preferably an integer of 0 to 2, further preferably 1 or 2. Most preferably, s is 0 or 1 and q is 2.

[1-13-e-6] In Formula (A)-IV or Formula (A1)-IV, more specifically, r is preferably 0.

67

[1-13-e-7] The ring A in Formula (I), Formula (A)-IV, or Formula (A2)-IV is preferably the Partial Structural Formula (A3)-IV:



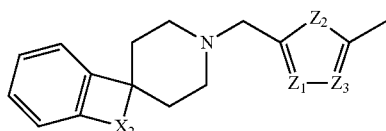
(A3)-IV

(where q and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; and R^{10f} is the same as defined in Formula (A2)-IV described in Aspect [1-13-e-3]).

In Formula (A3)-IV, preferably, R⁹ is a group optionally selected from a halogen atom, a cyano group, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), and a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s)). q is preferably an integer of 0 to 2. R^{10f} is preferably a hydrogen atom or a C₁₋₆ alkyl group, more preferably a hydrogen atom or a methyl group.

Specific examples of Formula (A3)-IV include 4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-yl and 4-methyl-2-(4-butoxy-3-chlorophenyl)thiazol-5-yl. Specific examples of Formula (A3)-IV of the present specification also include groups of the same formula as Formula (A3)-IV of the present specification in WO 2008/030520 pamphlet, that is, the corresponding groups in groups of Formula VIIC in p. 8, particularly the corresponding groups shown in Examples.

[1-13-e-8] The ring A in Formula (I), Formula (A)-IV, or Formula (A2)-IV is preferably the Partial Structural Formula (A4)-IV:



(A4)-IV

(where Z₁, Z₂, and Z₃ are the same as defined in Formula (A2)-IV described in Aspect [1-13-e-3] (with the proviso that R^{10e} and R^{10f} are independently a hydrogen atom, a methyl group, or a methoxy group); X₂ is —CH₂CH₂—, —CH=CH—, or —N(R_{z1})CH₂—; and R_{z1} is a hydrogen atom or a C₁₋₃ alkyl group).

In Formula (A4)-IV, preferably, Z₁ is —CR^{10e}—, R^{10e} is a hydrogen atom or a methyl group, Z₂ is a sulfur atom, Z₃ is —CR^{10f}—, and R^{10f} is a hydrogen atom. X₂ is —CH=CH— or —N(R_{z1})CH₂— and R_{z1} is a methyl group.

Specific examples of Formula (A4)-IV include 5-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)-2-thienyl, 4-methyl-5-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)-2-thienyl, and 5-(1-methylspiro[indolin-3,4'-piperidin]-1'-ylmethyl)-2-thienyl. Specific examples of Formula (A4)-IV of the present specification also include groups of the same formula as Formula (A4)-IV of the present specification in WO 2011/066183 pamphlet, particularly the corresponding groups shown in Examples.

[1-13-e-9] In Formula (A)-IV, Formula (A1)-IV, or Formula (A2)-IV, more preferable examples of R⁸ include a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is substituted with 1 to 5

68

—OH, 1 to 5 methoxy, 1 to 5 ethoxy, 1 to 5 methylsulfonyl, 1 to 5 sulfamoyl, 1 to 5 methylsulfamoyl, 1 to 5 dimethylsulfamoyl, 1 to 5 carbamoyl, 1 to 5 methylcarbamoyl, 1 to 5 dimethylcarbamoyl, 1 to 5 —NH₂, 1 to 5 acetylaminio, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, 1 to 5 5-oxo-2-pyrrolidinyl, or 1 to 5 3-methyloxetane-3-yl), a —CONR^{d4}R^{e4} group (R^{d4} is a hydrogen atom or a C₁₋₄ alkyl group; and R^{e4} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 —OH, 1 to 5 methoxy, 1 to 5 ethoxy, 1 to 5 methylsulfonyl, 1 to 5 sulfamoyl, 1 to 5 methylsulfamoyl, 1 to 5 dimethylsulfamoyl, 1 to 5 carbamoyl, 1 to 5 methylcarbamoyl, 1 to 5 dimethylcarbamoyl, 1 to 5 —NH₂, 1 to 5 acetylaminio, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, 1 to 5 5-oxo-2-pyrrolidinyl, or 1 to 5 3-methyloxetane-3-yl), (1,1-dioxidetetrahydro-2H-thiopyran-4-yl) oxy, and (pyrrolidine-1-yl)carbonyl. The substitution number of —OH, methoxy, ethoxy, methylsulfonyl, sulfamoyl, methylsulfamoyl, dimethylsulfamoyl, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, —NH₂, acetylaminio, methylsulfonylamino, 2-oxo-1-pyrrolidinyl, 5-oxo-2-pyrrolidinyl, or 3-methyloxetane-3-yl is preferably 1 to 2.

More specific examples of R⁸ include 2-hydroxyethoxy, 3-hydroxypropoxy, 3-hydroxybutoxy, 3-hydroxy-3-methylbutoxy, 2,3-dihydroxypropoxy, (2R)-2,3-dihydroxypropoxy, (2S)-2,3-dihydroxypropoxy, (3S)-3-hydroxybutoxy, (3R)-3-hydroxybutoxy, 3-hydroxy-2-hydroxymethylpropoxy, 3-hydroxy-2-hydroxymethyl-2-methylpropoxy, 2-aminoethoxy, 3-aminopropoxy, 2-(2-oxo-1-pyrrolidinyl)ethoxy, 3-(2-oxo-1-pyrrolidinyl)propoxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-ethoxyethoxy, 2-methyl sulfonylethoxy, 3-methylsulfonylpropoxy, (1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy, (4-hydroxy-1,1-dioxidetetrahydro-2H-thiopyran-4-yl)methoxy, (3-methyloxetane-3-yl)methoxy, 2-acetylaminio-ethoxy, 2-acetylaminio-ethoxy, 3-acetylaminio-propoxy, 2-methylsulfonylamino-ethoxy, 3-methylsulfonylamino-propoxy, 2-carbamoyl-ethoxy, 3-carbamoyl-propoxy, 2-methylcarbamoyl-ethoxy, 3-methylcarbamoyl-propoxy, 2-dimethylcarbamoyl-ethoxy, 3-dimethylcarbamoyl-propoxy, 2-sulfamoyl-ethoxy, 3-sulfamoyl-propoxy, 2-methylsulfamoyl-ethoxy, 3-methylsulfamoyl-propoxy, 2-dimethylsulfamoyl-ethoxy, 3-dimethylsulfamoyl-propoxy, N-(2-hydroxyethyl)carbamoyl, N-(2-methoxyethyl)carbamoyl, N-(2-hydroxyethyl)-N-methylcarbamoyl, N-(2-methoxyethyl)-N-methylcarbamoyl, N-(2-methylsulfonyl-ethyl)carbamoyl, N-(2-methylsulfonyl-ethyl)-N-methylcarbamoyl, and (pyrrolidine-1-yl)carbonyl.

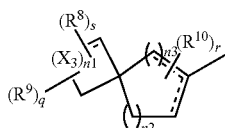
[1-13-e-10] In Formula (A)-IV, Formula (A1)-IV, Formula (A2)-IV, or Formula (A3)-IV, preferable examples of R⁹ and R¹⁰ independently include a halogen atom, a cyano group, a C₁₋₄ alkyl group (the C₁₋₄ alkyl group is optionally substituted with 1 to 5 halogen atom(s) or 1 to 5 —OH), a C₁₋₄ alkoxy group which is optionally substituted with 1 to 5 halogen atom(s), a C₂₋₄ alkenyl group, a C₂₋₅ alkanoyl group, a —S(O)_iR^a (i is 2; and R^a is a C₁₋₄ alkyl group) group, a —CONR^dR^e (R^d and R^e are independently a hydrogen atom or a C₁₋₄ alkyl group) group, and a —NR^{b1}R^{c1} group (R^{b1} and R^{c1} form, together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group; and in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an oxygen atom, a nitrogen atom, or a carbonyl group). More specific examples of R⁹ and R¹⁰ include a fluorine atom, a chlorine atom, a bromine atom, cyano, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, vinyl, acetyl, methylsulfonyl, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1-piperidinyl, 4-morpholinyl, and 2-oxooxazolidin-

69

3-yl. More preferable examples of R^9 , R^{9a} , and R^{9b} include a fluorine atom, methyl, and methoxy, and more preferable examples of R^{10} include methyl.

[1-13-e-11] In Formula (A)-IV, Formula (A1)-IV, or Formula (A2)-IV, preferable aspects of the ring A' moiety having $(R^8)_s$ and $(R^9)_q$ are the same groups as the groups having an aryl group or a heteroaryl group among the preferable aspects of L described in Aspect [1-1-d]. Specific examples of the ring A' moiety having $(R^8)_s$ and $(R^9)_q$ include the same groups as specific examples of the "aryl group which is optionally substituted with 1 to 5 substituent(s) RII" or the groups having a heteroaryl group among specific examples of the "heterocyclic group which is optionally substituted with 1 to 5 substituent(s) RII" that are described in Aspect [1]. More specific examples thereof include the same groups as the groups having benzene, naphthalene, pyridine, pyrimidine, thiophene, quinoline, or dibenzofuran.

[1-13-f] The ring A in Formula (I) is preferably Partial Structural Formula (A)-V:



(where q, r, s, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; n_1 is an integer of 0 to 4; n_2 is an integer of 1 to 4, n_3 is an integer of 0 to 2 (with the proviso that n_2+n_3 is an integer of 2 to 4); X_3 s are independently $—CR_{v1}R_{v2}—$ or $—NR_{v3}—$; R_{v1} , R_{v2} , and R_{v3} are independently a hydrogen atom, R^8 , or R^9 ; and the broken lines in the ring are a single bond or a double bond). In Formula (A)-V, the binding positions of R^8 , R^9 , and R^{10} are any positions at which they can be optionally bonded in the ring. Here, in Formula (A)-V, R^9 and R^{10} may be, in addition to the above description, $—OH$ or an oxo group, and R^8 may be, in addition to the above description, $—NHR_{v4}$ (R_{v4} is a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 group(s) optionally selected from $—OH$, a C_{1-6} alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C_{1-4} alkyl group(s) or 1 to 2 oxo group(s)), and a $—S(O)_iR^a$ (i is an integer of 0 to 2) group) or a C_{2-7} alkanoyl group (the C_{2-7} alkanoyl group is optionally substituted with 1 to 5 group(s) optionally selected from $—OH$, a C_{1-6} alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C_{1-4} alkyl group(s) or 1 to 2 oxo group(s)), and a $—S(O)_iR^a$ (i is an integer of 0 to 2) group)). These substituents are the same as or different from each other and are optionally substituted with 1 to 5 group(s) in the spiro ring.

[1-13-f-1] In Formula (A)-V, X_3 is preferably $—CR_{v1}R_{v2}—$ (R_{v1} and R_{v2} are the same as defined in Formula (A)-V).

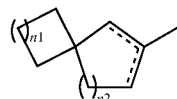
[1-13-f-2] In Formula (A)-V, preferably, n_1 is an integer of 0 to 4, n_2 is an integer of 1 to 3, and n_3 is 1 or 2. More preferably, n_1 is 2 or 3, n_2 is 1 or 2, and n_3 is 1.

[1-13-f-3] In Formula (A)-V, preferably, q is an integer of 0 to 2 and r is an integer of 0 to 2. More preferably, q and r are 0.

[1-13-f-4] In Formula (A)-V, s is preferably 0 or 1. More preferably, s is 0.

70

[1-13-f-5] More preferable examples of Formula (A)-V include Formula (A1)-V:



(where n_1 , n_2 , and the broken lines are the same as defined in Formula (A)-V). In Formula (A1)-V, most preferably, n_1 is 2 or 3 and n_2 is 1 or 2.

Specific examples of Formula (A)-V or Formula (A1)-V include spiro[4,5]dec-6-ene-7-yl, spiro[5,5]undec-2-yl, spiro[5,5]undec-1-ene-2-yl, and spiro[5,5]undec-2-ene-2-yl.

Specific examples of Formula (A)-V or Formula (A1)-V of the present specification also include groups of the same formula as Formula (A)-V or Formula (A1)-V of the present specification in WO 2009/054479 pamphlet, that is, the groups of the spiro ring AB in the item 2 in pp. 4 and 5, particularly the corresponding groups shown in Examples.

[1-13-f-6] In Formula (A)-V, preferable examples of R^9 and R^{10} independently include a halogen atom, a C_{1-4} alkyl group which is optionally substituted with 1 to 5 halogen atom(s), a C_{1-4} alkoxy group which is optionally substituted with 1 to 5 halogen atom(s), an $—OH$ group, and an oxo group. More specific examples of R^9 and R^{10} include a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, and $—OH$. More preferable examples of R^9 include a fluorine atom, methyl, methoxy, and $—OH$, and more preferable examples of R^{10} include methyl and $—OH$.

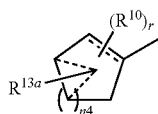
Specific examples of Formula (A)-V of the present specification also include the corresponding groups of the spiro ring AB substituted with a substituent (an $—OH$ group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, or an oxo group) in a formula of Formula [Ia] of WO 2009/054479 pamphlet) as a group substituted with R^9 or R^{10} in Formula (A)-V, particularly the corresponding groups shown in Examples.

[1-13-f-7] In Formula (A)-V, preferable examples of R^8 s independently include a C_{1-6} alkoxy group (the C_{1-6} alkoxy group is substituted with 1 to 5 group(s) optionally selected from $—OH$, a C_{1-6} alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C_{1-4} alkyl group(s) or 1 to 2 oxo group(s)), and a $—S(O)_iR^a$ (i is an integer of 0 to 2) group), a $—CONR^{d3}R^{e3}$ group (R^{d3} is a hydrogen atom or a C_{1-4} alkyl group; and R^{e3} is a C_{1-6} alkyl group (the C_{1-6} alkyl group is substituted with 1 to 5 group(s) optionally selected from $—OH$, a C_{1-6} alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C_{1-4} alkyl group(s) or 1 to 2 oxo group(s)), and a $—S(O)_iR^a$ (i is an integer of 0 to 2) group)), an alkoxy group, a non-aromatic heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 2 oxo group(s)), and a non-aromatic heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 2 oxo group(s)), and $—NHR_{v4}$ (R_{v4} is a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 group(s) optionally selected from $—OH$, a C_{1-6} alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C_{1-4} alkyl group(s) or 1 to 2 oxo group(s)), and a $—S(O)_iR^a$ (i is an integer of 0 to 2) group)).

71

optionally selected from —OH, a C₁₋₆ alkoxy group, a non-aromatic heterocyclic group (the heterocyclic group is optionally substituted with 1 to 2 C₁₋₄ alkyl group(s) or 1 to 2 oxo group(s)), and a —S(O)_iR^a (i is an integer of 0 to 2) group)). More specific examples of R⁸ include a C₁₋₆ alkoxy group which is substituted with 1 to 2 —OH, 1 to 2 methoxy, 1 to 2 ethoxy, 1 to 2 2-oxo-1-pyrrolidinyl, 1 to 2 5-oxo-2-pyrrolidinyl, 1 to 2 3-methyloxetane-3-yl, or 1 to 2 methylsulfonyl; a —CONR^{d4}R^{e4} group (R^{d4} is a hydrogen atom or a C₁₋₄ alkyl group; and R^{e4} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is substituted with 1 to 5 —OH, 1 to 5 methoxy, 1 to 5 ethoxy, 1 to 5 2-oxo-1-pyrrolidinyl, 1 to 5 5-oxo-2-pyrrolidinyl, 1 to 5 3-methyloxetane-3-yl, or 1 to 5 methylsulfonyl)), an aralkyloxy group, (1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy, (pyrrolidine-1-yl)carbonyl, and —NHR_{v4} (R_{v4} is a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 2 —OH, 1 to 2 ethoxy, 1 to 2 2-oxo-1-pyrrolidinyl, 1 to 2 5-oxo-2-pyrrolidinyl, 1 to 2 3-methyloxetane-3-yl, or 1 to 2 methylsulfonyl) or a C₂₋₇ alkanoyl group (the C₂₋₇ alkanoyl group is optionally substituted with 1 to 2 —OH, 1 to 2 ethoxy, 1 to 2 2-oxo-1-pyrrolidinyl, 1 to 2 5-oxo-2-pyrrolidinyl, 1 to 2 3-methyloxetane-3-yl, or 1 to 2 methylsulfonyl)).

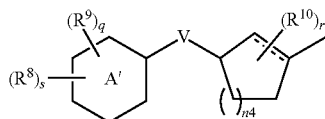
[1-13-f-8] The ring A in Formula (I) is preferably Partial Structural Formula (AA)-V:



(where R^{13a} is the same as defined in Formula (AA) described in Aspect [1-13-d]; r is the same as defined in Formula (A) described in Aspect [1-13-c]; R¹⁰ is the same as defined in Formula (A)-V described in Aspect [1-13-f]; n₄ is an integer of 1 to 3; and the broken lines are a single bond, a double bond, or the binding position of R^{13a}).

[1-13-f-9] The preferable aspects of R^{13a} in Formula (AA)-V are the same as the preferable aspects described in Aspects [1-13-d-11] to [1-13-d-11-3]. More preferably, R^{13a} is a group of Formula (A')-V—.

[1-13-f-10] Preferable examples of the ring A in Formula (I) or Formula (AA)-V include Formula (AA1)-V:



(where q, r, s, the ring A', V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; R¹⁰ and the broken line are the same as defined in Formula (A)-V described in Aspect [1-13-f]; and n₄ is the same as defined in Formula (AA)-V).

[1-13-f-11] In Formula (AA)-V or Formula (AA1)-V, n₄ is preferably 1 or 2, more preferably 2.

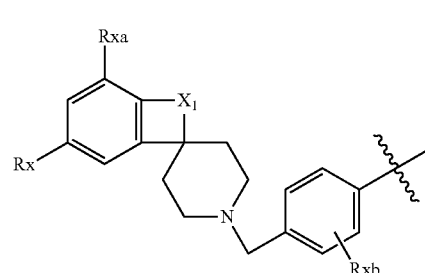
[1-13-f-12] In Formula (AA)-V or Formula (AA1)-V, r is preferably an integer of 0 to 2. In Formula (AA1)-V, q is preferably an integer of 0 to 3, more preferably an integer of 0 to 2. s is preferably 0 or 1. More preferably, any one of q and s is 1 or more.

72

[1-13-f-13] In Formula (AA1)-V, the preferable aspects of the ring A', R⁸, and R⁹ are the same as the preferable aspects described in Aspects [1-13-c-2], [1-13-c-7] to [1-13-c-7-2], and [1-13-c-8]. The preferable aspects of the ring A' moiety having (R⁸)_s and (R⁹)_q are the same as the preferable aspects described in Aspect [1-13-c-10].

In Formula (AA)-V or Formula (AA1)-V, the preferable aspects of R¹⁰ are the same as the preferable aspects described in Aspect [1-13-f-6].

[1-13-g] The ring A in Formula (I) is preferably Partial Structural Formula (A)-VI:



(where R_x, R_{xa}, and X₁ are the same as defined in Formula (SP) described as the “substituted spiro piperidinyl group” in Aspect [1]; and R_{xb} is a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, C₁₋₃ alkyl, trifluoromethyl, and methoxy).

[1-13-g-1] In Formula (A)-VI, preferably, at least any one of R_x and R_{xa} is a hydrogen atom. More preferably, R_{xa} is a hydrogen atom and R_x is a group selected from a hydrogen atom, a fluorine atom, methyl, trifluoromethyl, and methoxy, or R_{xa} is a hydrogen atom or a chlorine atom and R_x is a hydrogen atom, or both of R_x and R_{xa} are a hydrogen atom.

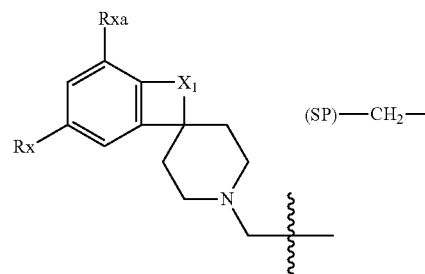
In Formula (A)-V₁, R_{xb} is preferably a group selected from a hydrogen atom, methyl, trifluoromethyl, and methoxy, more preferably a hydrogen atom.

In Formula (A)-V₁, X₁ is preferably —CH(R_y)CH₂—, —C(R_y)=CH—, or —N(R_z)CH₂, more preferably —C(R_y)=CH— or —N(R_z)CH₂.

In Formula (A)-V₁, R_y is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

In Formula (A)-VI, R_z is preferably a hydrogen atom or C₁₋₃ alkyl, more preferably methyl.

Specifically, in Aspect [1-13-g], examples of Partial Structural Formula (SP)—CH₂—:

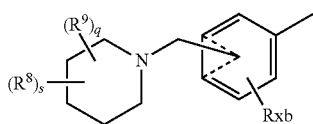


in Formula (A)-VI include a group selected from any of spiro[indan-1,4'-piperidin]-1'-ylmethyl, (1'H-spiro[inden-1,4'-piperidin]-1'-yl)methyl, 1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-ylmethyl, (1-methyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, {1-(1-methylethyl)-1,2-

73

dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, (1-phenyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, (2,3-dihydro-1'H-spiro[inden-1,4'-piperidin]-1'-yl)methyl, (7-chloro-1-methyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, (5-fluoro-1-methyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, (5-methoxy-1-methyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, (1,5-dimethyl-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, [1-methyl-5-(trifluoromethyl)-1,2-dihydro-1'H-spiro[indol-3,4'-piperidin]-1'-yl)methyl, and (3-oxo-2,3-dihydro-1'H-spiro[inden-1,4'-piperidin]-1'-yl)methyl.

[1-13-g-2] Preferable examples of the ring A in Formula (I) include Partial Structural Formula (AA)-VI:

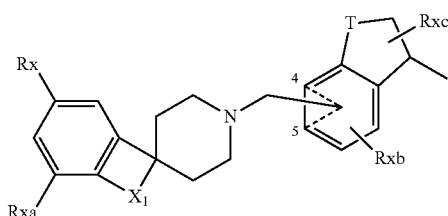


(AA)-VI

(where q, s, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; R_{xb} is the same as defined in Formula (A)-VI described in Aspect [1-13-g]; and the broken lines indicate the binding position of a piperidinylmethyl group).

The preferable aspects of q, s, R⁸, and R⁹ in Formula (AA)-VI are the same as the preferable aspects described in Aspects [1-13-c-3], [1-13-c-5], [1-13-c-7] to [1-13-c-7-2], or [1-13-c-8].

[1-13-h] The ring A in Formula (I) is preferably Partial Structural Formula (A)-VII:

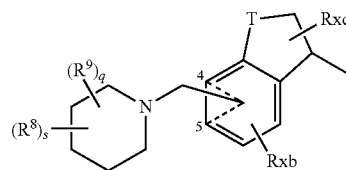


(A)-VII

(where T is the same as defined in Formula (AA) described in Aspect [1-13-d]; R_x, R_{xa}, and X₁ are the same as defined in Formula (SP) described as the "substituted spiropiperidinyl group" in Aspect [1]; R_{xb} is the same as defined in Formula (A)-VI described in Aspect [1-13-g]; R_{xc} is a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, C₁₋₃ alkyl, trifluoromethyl, and methoxy; and the broken lines and the FIGS. 4 and 5 indicate the binding position of the substituted spiropiperidinylmethyl group).

[1-13-h-1] Preferable examples of the ring A in Formula (I) include Partial Structural Formula (AA)-VII:

74



(AA)-VII

(where T is the same as defined in Formula (AA) described in Aspect [1-13-d]; q, s, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; R_{xb} is the same as defined in Formula (A)-VI described in Aspect [1-13-g]; R_{xc} is the same as defined in Formula (A)-VII described in Aspect [1-13-h]; and the broken lines indicate the binding position of the piperidinylmethyl group).

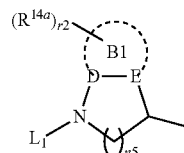
The preferable aspects of q, s, R⁸, and R⁹ in Formula (AA)-VII are the same as the preferable aspects described in Aspects [1-13-c-3], [1-13-c-5], [1-13-c-7] to [1-13-c-7-2], or [1-13-c-8].

[1-13-i] Preferable examples of the ring A in Formula (I) include phthalazinyl which is optionally substituted with 1 to 5 L(s).

Specific examples of phthalazinyl which is optionally substituted with 1 to 5 L(s) include 4-chloro-1-phthalazinyl, 4-trifluoromethyl-1-phthalazinyl, 4-cyano-1-phthalazinyl, and 4-cyclopropylmethoxy-1-phthalazinyl.

Specific examples of the ring A of the present specification also include the groups of G in Formula (I) and the like in WO 2010/091176 pamphlet, particularly the corresponding groups shown in Examples.

[1-13-j] Preferable examples of the ring A in Formula (I) include Partial Structural Formula (A)-VIII:



(A)-VIII

(where r2 is an integer of 0 to 4; n5 is 1 or 2; D is —CO—CR^{14b}R^{14c}— or —(CR^{14b}R^{14c})_m (m is 1 or 2)-; E is —CR^{14d}R^{14e}—;

L₁ is a group optionally selected from a C₁₋₁₀ alkyl group (the C₁₋₁₀ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), an aryl group (the aryl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 C₁₋₆ alkyl group(s), or 1 to 5 halogenated C₁₋₆ alkyl group(s)), a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 C₁₋₆ alkyl group(s), or 1 to 5 halogenated C₁₋₆ alkyl group(s)), an aralkyl group (the aralkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 C₁₋₆ alkyl group(s), or 1 to 5 halogenated C₁₋₆ alkyl group(s)), a heteroarylalkyl group (the heteroarylalkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 C₁₋₆ alkyl group(s), or 1 to 5 halogenated C₁₋₆ alkyl group(s)), a C₂₋₇ alkanoyl group, and a —S(O)_iR^a (i is an integer of 0 to 2; and R^a is the same as defined in Formula (I)) group;

R^{14a}s are independently a halogen atom, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5

75

halogen atom(s)), or a C₁₋₆ alkoxy group (the C₁₋₆ alkoxy group is optionally substituted with 1 to 5 halogen atom(s)); and

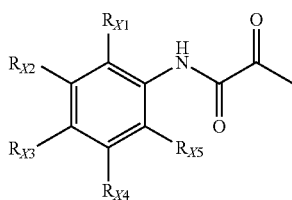
R^{14b}, R^{14c}, R^{14d}, and R^{14e} are independently a hydrogen atom, a halogen atom, or a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s)); and R^{14c} and R^{14e} optionally form, together with a carbon atom to which they are bonded, a 5- to 6-membered aryl group or heteroaryl group (ring B 1)).

In Formula (A)-VII₁, L₁ is preferably a group optionally selected from a C₁₋₄ alkyl group (the C₁₋₄ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), a heteroaryl group (the heteroaryl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 C₁₋₄ alkyl group(s), or 1 to 5 halogenated C₁₋₄ alkyl group(s)), and a —S(O)_iR^a (i is an integer of 0 to 2; and R^a is the same as defined in Formula (I)) group.

Specific examples of Formula (A)-VIII include 1,2,3,4-tetrahydro-1-oxo-2-(2,2,2-trifluoroethyl)-4-isoquinolyl, 2-cyclopropylmethyl-1,2,3,4-tetrahydro-1-oxo-4-isoquinolyl, 1,2,3,4-tetrahydro-2-(2-methylpropyl)-1-oxo-4-isoquinolyl, 1-(5-fluoro-2-pyridinyl)-3-piperidinyl, 1-(5-trifluoromethyl-2-pyridinyl)-3-piperidinyl, 1,2,3,4-tetrahydro-1-methylsulfonyl-4-quinolyl, 8-fluoro-1,2,3,4-tetrahydro-1-methylsulfonyl-4-quinolyl, 1,2,3,4-tetrahydro-1-(2,2,2-trifluoroethyl)-4-quinolyl, and 8-fluoro-1,2,3,4-tetrahydro-1-(2,2,2-trifluoroethyl)-4-quinolyl.

Specific examples of the ring A and Formula (A)-VIII of the present specification also include the cyclic group containing D and E in Formula (I) and the like in WO 2010/085525 pamphlet, particularly the corresponding groups shown in Examples.

[1-13-k] Preferable examples of the ring A in Formula (I) include a 2-phenylamino-2-oxoacetyl group which is optionally substituted with 1 to 5 L(s) and more preferable examples thereof include Partial Structural Formula (A)-IX:



(where R_{X3} is a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₈ alkyl group (the C₁₋₈ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), a trifluoromethoxy group, a phenyl group, and a —COOR^f group; R_{X1} and R_{X5} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), a phenyl group, and a —COOR^f group; R_{X2} and R_{X4} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group (the C₁₋₆ alkyl group is optionally substituted with 1 to 5 halogen atom(s)), and a —COOR^f group; and R^f is a hydrogen atom or a C₁₋₆ alkyl group).

In Formula (A)-IX, R_{X3} is preferably a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a trifluoromethyl group, a methoxycarbonyl group, or a phenyl group. R_{X2} and R_{X5} are preferably independently a hydrogen atom, a halogen atom, a methyl group, a trifluoromethyl group, a methoxycarbonyl

76

group, or a phenyl group. R_{X2} and R_{X4} are preferably independently a hydrogen atom, a halogen atom, or a trifluoromethyl group.

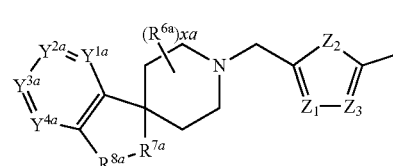
Specific examples of Formula (A)-IX include 2-((2-bromo-4-isopropylphenyl)amino)-2-oxoacetyl, 2-((4-isopropyl-2-(trifluoromethyl)phenyl)amino)-2-oxoacetyl, 2-((2,4-bis(trifluoromethyl)phenyl)amino)-2-oxoacetyl, and 2-((4-bromo-3-chlorophenyl)amino)-2-oxoacetyl.

Specific examples of the ring A and Formula (A)-IX of the present specification also include the groups of the same formula as Formula (A)-IX of the present specification in Formula (I) in WO 2009/039943 pamphlet, particularly the corresponding groups shown in Examples.

[1-13-1] In the preferable Aspects [1-13-e-8], [1-13-g], and [1-13-h] of the ring A in Formula (I), an aspect in which each spiropiperidine ring (SP) is replaced with the above-described another spiropiperidine ring (SP') is also a preferable aspect.

Accordingly, it can be understood that examples of the preferable aspect of the ring A in Formula (I) of the present invention include, in addition to Aspects [1-13-e-8], [1-13-g], and [1-13-h], [1-13-e-8a], [1-13-ga], and [1-13-ha] below.

[1-13-e-8a] The ring A in Formula (I) is preferably Partial Structural Formula (A5)-IVa:



(A5)-IVa

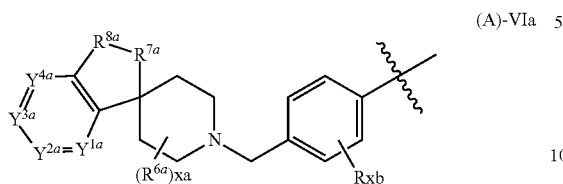
(where Z₁, Z₂, and Z₃ are the same as defined in Formula (A2)-IV described in Aspect [1-13-e-3]; and R^{6a}, R^{7a}, R^{8a}, x_a, and Y^{1a} to Y^{4a} are the same as defined in the above Formula (SP')).

In Formula (A5)-IVa, preferably, Z₁ is —CR^{10e}—, R^{10e} is a hydrogen atom or a methyl group, Z₂ is a sulfur atom, Z₃ is —CR^{10f}—, and R^{10f} is a hydrogen atom. X₂ is —CH=CH— or —N(R_{Z1})CH₂—, and R_{Z1} is a methyl group.

Specific examples of Formula (A5)-IVa include 5-(spiro[isobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[benzofuran-3(2H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(3-oxospiro[4-azaisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(3-oxospiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, 5-(spiro[6-fluoro-5-azaisobenzofuran-1(3H),4'-piperidin]-1'-ylmethyl)-2-thienyl, and 5-(7-fluoro-1H-spiro[fluoro[3,4-c]pyridin-3,4'-piperidin]-1'-ylmethyl)-2-thienyl.

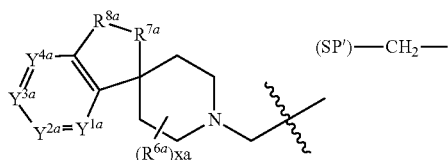
77

[1-13-ga] The ring A in Formula (I) is preferably Formula (A)-VIa:



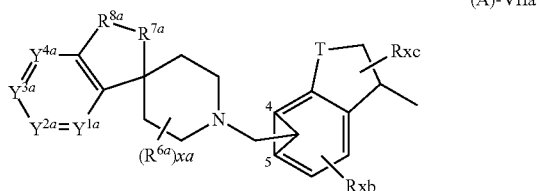
(where R_{xb} is a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, C_{1-3} alkyl, trifluoromethyl, and methoxy, more preferably, a hydrogen atom; and R^{6a} , R^{7a} , R^{8a} , x_a , and Y^{1a} to Y^{4a} are the same as defined in Formula (SP')):

Specific examples of the ring A include rings in which Partial Structural Formula (SP')—CH₂—:



in Formula (A)-VIa is spiro[isobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[benzofuran-3(2H),4'-piperidin]-1-yl)methyl, (3-oxospiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoro-6-azaisobenzofuran-1(3M), 4'-piperidin]-1-yl)methyl, or (7-fluoro-1H-spiro[fluoro[3,4-c]pyridin-3,4'-piperidin]-1-yl)methyl.

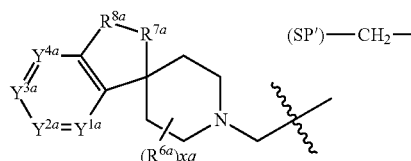
[1-13-ha] The ring A in Formula (I) is preferably Partial Structural Formula (A)-VIIa:



(where T is the same as defined in Formula (AA) described in Aspect [1-13-d]; the definitions of R^{6a} , R^{7a} , R^{8a} , x_a , and Y^{1a} to Y^{4a} correspond to the definitions of R^6 , R^7 , R^8 , x , and Y^1 to Y^4 respectively in Formula [II] in WO 2002/088989 pamphlet; R_{xb} is a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, C_{1-3} alkyl, trifluoromethyl, and methoxy, preferably a hydrogen atom; R_{xc} is a group selected from a hydrogen atom, a fluorine atom, a chlorine atom, C_{1-3} alkyl, trifluoromethyl, and methoxy, preferably a hydrogen atom; and the broken lines and the FIGS. 4 and 5 indicate the binding position of the substituted spiro-piperidinylmethyl group).

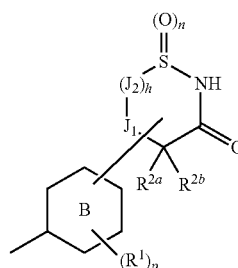
78

Specific examples of the ring A include rings in which Partial Structural Formula (SP')—CH₂—:



in Formula (A)-VIIa is (spiro[isobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[benzofuran-3(2H), 4'-piperidin]-1-yl)methyl, (3-oxospiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[6-fluoroisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, (spiro[5-fluoro-6-azaisobenzofuran-1(3H),4'-piperidin]-1-yl)methyl, or (7-fluoro-1H-spiro[fluoro[3,4-c]pyridin-3,4'-piperidin]-1-yl)methyl.

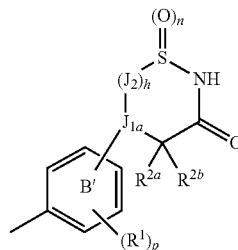
[1-14] The group having the ring B and the cyclic amide structure of Formula (I) according to Aspect [1] is Partial Structural Formula (B):



(where n , p , h , the ring B, J_1 , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]).

[1-14-a] In Formula (B), when the ring B is a monocyclic ring, the ring B is preferably bonded to J_1 .

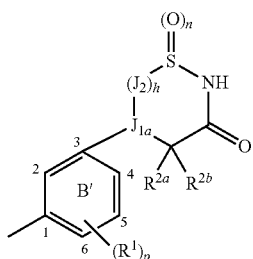
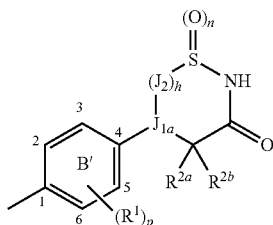
[1-14-a-1] In Formula (B), when the ring B is a benzene ring, a pyridine ring, or a pyrimidine ring, Formula (B) is preferably Formula (B)-1:



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; the ring B' is a benzene ring, a pyridine ring, or a pyrimidine ring; and J_{1a} is CR^{11a} or a nitrogen atom).

79

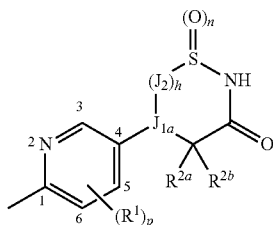
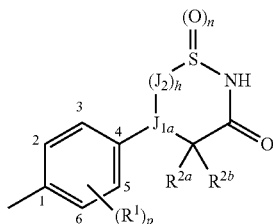
[1-14-a-2] More preferable examples of Formula (B) include Formula (B1) and Formula (B2):



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); and the ring B' and J_{1a} are the same as defined in Formula (B)-1). When the binding position with the linker moiety containing X is determined as 1-position, in Formula (B1), R^1 can be bonded at 2-position, 3-position, 5-position, and 6-position, and in Formula (B2), R^1 can be bonded at 2-position, 4-position, 5-position, and 6-position.

[1-14-a-3] Formula (B) or Formula (B)-1 is preferably Formula (B1).

[1-14-a-4] More preferable examples of Formula (B) or Formula (B)-1 include Formula (B1a) and Formula (B1b):



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); and J_{1a} is the same as defined in Formula (B)-1).

[1-14-a-5] Further preferable examples of Formula (B) or Formula (B)-1 include Formula (B1a).

[1-14-b] When in Formula (B), the ring B is Formula (BB1) or Formula (BB2), Formula (B) is Formula (BB1)-1 or Formula (BB2)-1:

80

(BB1)-1

(B1) 5

10

(B2) 15

20

25

30

35

(where n , p , h , J_1 , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; and G , W_1 , W_2 , and W_3 are the same as in Formula (BB1) and Formula (BB2) described in Aspect [1-10]). Specifically, Formula (B) is preferably Formula (BB1)-1a, Formula (BB1)-1b, Formula (BB2)-1a, or Formula (BB2)-1b:

(BB1)-1a

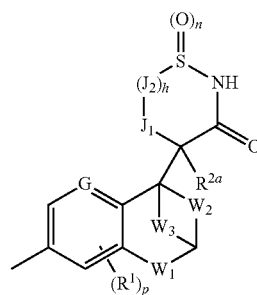
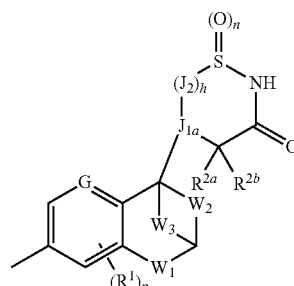
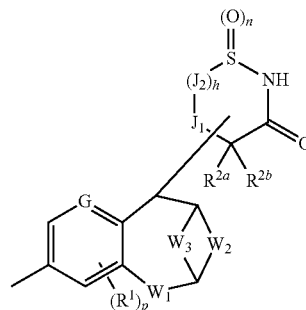
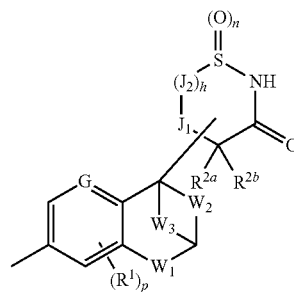
(B1a) 40

45

(B1b) 50

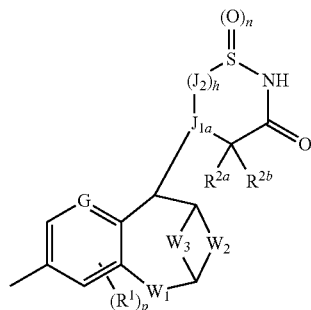
55

(BB1)-1b

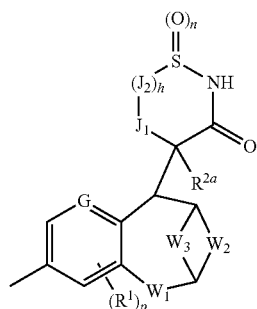


81

-continued



(BB2)-1a



(BB2)-1b

(where n , p , h , J_1 , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1; and G , W_1 , W_2 , and W_3 are the same as in Formula (BB1) and Formula (BB2) described in Aspect [1-10]). When J_2 is $-\text{CR}^{12a}\text{R}^{12b}-$, a structure in which Formula (BB1) or Formula (BB2) is bonded to J_2 adjacent to S in the cyclic amide structure, is also preferred.

[1-14-c] When the ring A is Formula (A) described in Aspect [1-13-c] and the ring A'-V— is bonded at the m-position relative to the binding position with the linker moiety containing X, specifically when the ring A is Formula (A1a), Formula (A1b), Formula (A1c), or Formula (A1)-1-1 described in Aspect [1-13-c-3-1] or Aspect [1-13-c-11], in Formula (B)-1, an isothiazolyl group is preferably bonded at the p-position relative to the binding position with the linker moiety containing X. When the ring A is Formula (AA1) described in Aspect [1-13-d-4] and R^{13a} is bonded at 4-position, or the ring A is Formula (AA1b) described in Aspect [1-13-d-7] and R^{13a} is bonded at 7-position, specifically also when the ring A is Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, or Formula (AA1b)-1 described in Aspects [1-13-d-5] to [1-13-d-7-1], in Formula (B)-1, an isothiazolyl group is preferably bonded at the p-position relative to the binding position with the linker moiety containing X. Further, also when the ring A is Formula (A)-IV, Formula (A1)-IV, Formula (A2)-IV, Formula (A3)-IV, or Formula (A4)-IV described in Aspects [1-13-e] to [1-13-e-8], Formula (A)-V, Formula (A1)-V, Formula (AA)-V, or Formula (AA1)-V described in Aspects [1-13-f] to [1-13-f-10], or Formula (A)-VI or Formula (AA)-VI described in Aspects [1-13-g] to [1-13-g-2], in Formula (B)-1, an isothiazolyl group is preferably bonded at the p-position relative to the binding position with the linker moiety containing X.

[1-14-c-1] When the ring A is Formula (A) described in Aspect [1-13-c] and the ring A'-V— is bonded at the p-position relative to the binding position with the linker moiety containing X, specifically when the ring A is Formula (A1)-1-2 described in Aspect [1-13-c-12], in Formula (B)-1, an

82

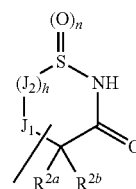
isothiazolyl group is preferably bonded at the m-position relative to the binding position with the linker moiety containing X.

[1-14-d] In Formula (B), Formula (B)-1, Formula (B1), Formula (B2), Formula (B1a), Formula (B1b), Formula (BB1)-1, Formula (BB2)-1, Formula (BB1)-1a, Formula (BB1)-1b, Formula (BB2)-1a, or Formula (BB2)-1b, R^1 is preferably a halogen atom, a C_{1-4} alkyl group which is optionally substituted with 1 to 5 halogen atom(s), a C_{1-4} alkoxy group which is optionally substituted with 1 to 5 halogen atom(s), or a cyano group, and more specifically, R^1 is preferably a fluorine atom, a chlorine atom, a bromine atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, trifluoromethoxy, or cyano, p is preferably 0 or 1, more preferably 0.

In Formula (B), Formula (B)-1, Formula (B1), Formula (B2), Formula (B1a), Formula (B1b), Formula (BB1)-1, Formula (BB2)-1, Formula (BB1)-1a, Formula (BB1)-1b, Formula (BB2)-1a, or Formula (BB2)-1b, R^{2a} and R^{2b} are preferably a hydrogen atom, a halogen atom, or a C_{1-4} alkyl group. More specifically, R^{2a} and R^{2b} are preferably a hydrogen atom, a fluorine atom, a chlorine atom, a bromine atom, or methyl, and more preferably, any one of R^{2a} and R^{2b} is a hydrogen atom. Further preferably, both of R^{2a} and R^{2b} are a hydrogen atom.

In Formula (B), Formula (B)-1, Formula (B1), Formula (B2), Formula (B1a), Formula (B1b), Formula (BB1)-1, Formula (BB2)-1, Formula (BB1)-1a, Formula (BB1)-1b, Formula (BB2)-1a, or Formula (BB2)-1b, h is preferably 0 or 1 and n is preferably 1 or 2. When J_{1a} is CR^{11a} and h is 0, n is more preferably 1. When J_{1a} is a nitrogen atom and h is 0, n is more preferably 2. When h is an integer of 1 to 3, n is more preferably 2.

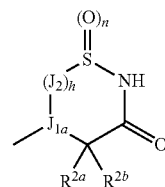
[1-14-e] The cyclic amide structure bonded to the ring B in Formula (I), Formula (B), Formula (BB1)-1, or Formula (BB2)-1 is Partial Structural Formula (B-Het):



(B-Het)

(where n , h , J_1 , J_2 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]). In Formula (B-Het), the ring B can be bonded at any position in the ring, specifically to a carbon atom to which R^{2a} and R^{2b} are bonded, J_1 , or J_2 .

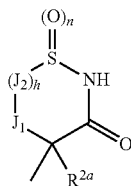
In Formula (I) or Formula (B), Formula (B-Het) is preferably Formula (B-Het)-1 or (B-Het)-2:



(B-Het)-1

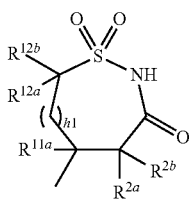
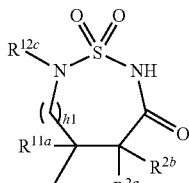
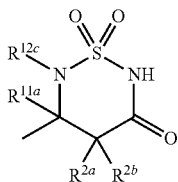
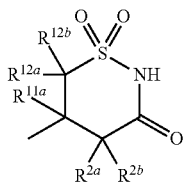
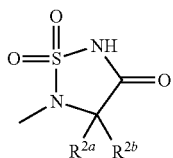
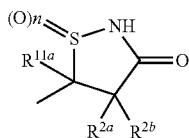
83

-continued



(where n , h , J_1 , J_2 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; and J_{1a} is the same as defined in Formula (B)-1).

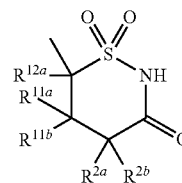
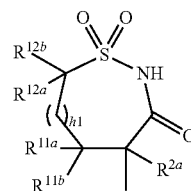
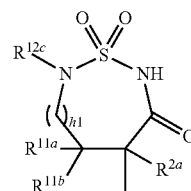
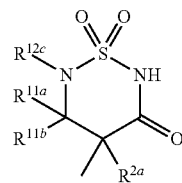
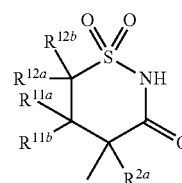
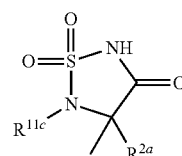
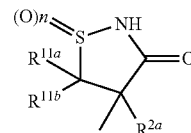
[1-14-e-1] More preferable examples of Formula (B-Het) or Formula (B-Het)-1 include Formula (B-Het)-1a, Formula (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, and Formula (B-Het)-1f:



84

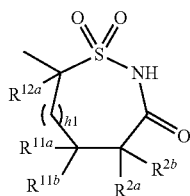
(where n , R^{2a} , R^{2b} , R^{11a} , R^{12a} , R^{12b} , and R^{12c} are the same as defined in Formula (I) described in Aspect [1]; and $h1$ is 1 or 2).

More preferable examples of Formula (B-Het) or Formula (B-Het)-2 include Formula (B-Het)-2a, Formula (B-Het)-2b, Formula (B-Het)-2c, Formula (B-Het)-2d, Formula (B-Het)-2e, Formula (B-Het)-2f, Formula (B-Het)-3c, and Formula (B-Het)-3f:



85

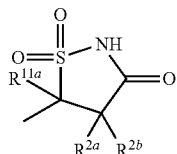
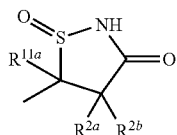
-continued



(where n , R^{2a} , R^{2b} , R^{11a} , R^{12a} , R^{12b} , R^{11c} , and R^{12c} are the same as defined in Formula (I) described in Aspect [1]; and $h1$ is 1 or 2).

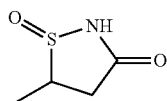
In Formula (I) according to Aspect [1], a compound in which the cyclic amide structure bonded to the ring B (that is, Formula (B-Het)) is Formula (B-Het)-1a is Formula (I)-1a. Similarly, the compound having Formula (B-Het)-1b is Formula (I)-1b; the compound having Formula (B-Het)-1c is Formula (I)-1c; the compound having Formula (B-Het)-1d is Formula (I)-1d; the compound having Formula (B-Het)-1e is Formula (I)-1e; the compound having Formula (B-Het)-1f is Formula (I)-1f; the compound having Formula (B-Het)-2a is Formula (I)-2a; the compound having Formula (B-Het)-2b is Formula (I)-2b; the compound having Formula (B-Het)-2c is Formula (I)-2c; the compound having Formula (B-Het)-2d is Formula (I)-2d; the compound having Formula (B-Het)-2e is Formula (I)-2e; the compound having Formula (B-Het)-2f is Formula (I)-2f; the compound having Formula (B-Het)-3c is Formula (I)-3c; and the compound having Formula (B-Het)-3f is Formula (I)-3f.

In Formula (B-Het)-1a, n is preferably 1 or 2, and specifically, Formula (B-Het)-1a is Formula (B-Het)-1a1 or Formula (B-Het)-1a2:



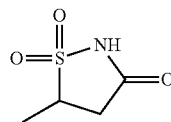
(where R^{2a} , R^{2b} , and R^{11a} are the same as defined in Formula (I)).

[1-14-e-2] In each formula used for a compound in each aspect of Aspect [1], the Formula (B-Het) moiety can be accordingly selected from, for example, Formulae (het1) to (het9):



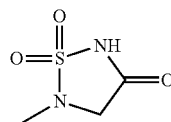
(B-Het)-3f

5



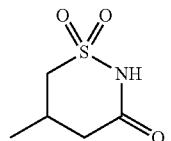
(het2)

10



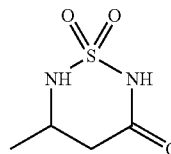
(het3)

15



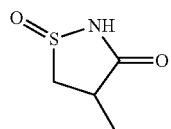
(het4)

20



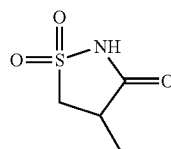
(het5)

25



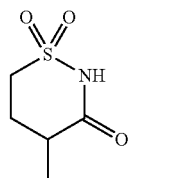
(het6)

30



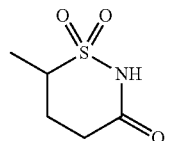
(het7)

40



(het8)

45



(het9)

50

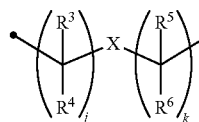
The Formula (B-Het) moiety is particularly preferably Formulae (het1) to (het5) above.

55

[1-15] In a combination of j , k , X , R^3 , R^4 , R^5 , and R^6 , in Formula (I), the linker moiety containing X bonded to the ring A and the ring B is Partial Structural Formula (C):

60

(het1)



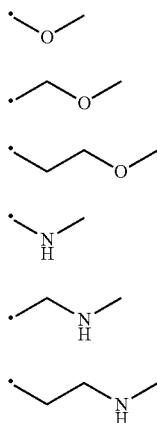
(C)

65

87

(where j, k, X, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I) described in Aspect [1]; and ● is a single bond with the ring A).

Preferable specific examples of Formula (C) include Formula (c1) to Formula (c6).



[1-15-a] More preferably, Formula (C) is Formula (c1), Formula (c2), Formula (c4), or Formula (c5).

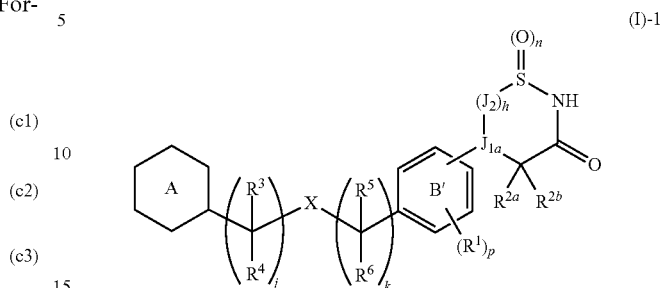
[1-15-b] When the ring A is a monocyclic ring or a spiro ring, that is, when the ring A is a phenyl group, a monocyclic heterocyclic group, a cycloalkyl group, a cycloalkenyl group, or a spiro ring group, specifically, when the ring A is Formula (A), Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), Formula (A1c), Formula (A1)-1-1, or Formula (A1)-1-2 described in Aspects [1-13-c] to [1-13-c-12], Formula (A)-IV, Formula (A1)-IV, Formula (A2)-IV, Formula (A3)-IV, or Formula (A4)-IV described in Aspects [1-13-e] to [1-13-e-8], Formula (A)-V, Formula (A1)-V, Formula (AA)-V, or Formula (AA1)-V described in Aspects [1-13-f] to [1-13-f-10], Formula (A)-VI or Formula (AA)-VI described in Aspects [1-13-g] to [1-13-g-2], or Formula (A5)-IVa or Formula (A)-VIa described in Aspect [1-13-e-8a] or [1-13-ga], Formula (C) is further preferably Formula (c2) or Formula (c5), most preferably Formula (c2).

[1-15-c] When the ring A is a fused ring, that is, when the ring A is a ring-fused aryl group, a partly hydrogenated ring-fused aryl group, a ring-fused heteroaryl group, a partly hydrogenated ring-fused heteroaryl group, or a ring-fused non-aromatic heterocyclic group, specifically when the ring A is Formula (AA), Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), or Formula (AA1b)-1 described in Aspects [1-13-d] to [1-13-d-7-1], Formula (A)-VII or Formula (AA)-VII described in Aspect [1-13-h] or [1-13-h-1], a phthalazinyl group described in Aspect [1-13-i], Formula (A)-VIII described in Aspect [1-13-j], or Formula (A)-VIIa described in Aspect [1-13-ha], Formula (C) is further preferably Formula (c1) or Formula (c4), most preferably Formula (c1).

[1-15-d] When the ring A is a 2-phenylamino-2-oxoacetyl group, specifically when the ring A is Formula (A)-IX described in Aspect [1-13-k], the linker moiety is preferably —NR⁷—, more preferably Formula (c4).

88

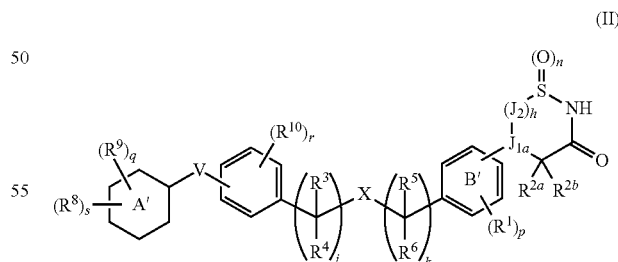
[1-16] The compound of Formula (I) according to Aspect [1] is preferably a compound of Formula (I)-1:



(where n, p, h, j, k, the ring A, X, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I) described in Aspect [1]; and the ring and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1] (with the proviso that a compound that is 5-[4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one; a compound in which a saturated cyclic amide structure having —S(O)_n—NH—CO— is 1,1-dioxo-1,2-thiazolidin-3-one, the ring B' is a benzene ring, k is 1, and in the ring B', the linker moiety containing X and the cyclic amide structure are at the p-position; and a compound in which the cyclic amide structure is 1,1-dioxo-1,2,5-thiadiazolidin-3-one, and in the ring B', the cyclic amide structure is bonded to an atom adjacent to an atom to which the linker containing X is bonded, are excluded)).

More specifically, the preferable aspects of n, p, h, j, k, the ring A, the ring B', X, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (I)-1 corresponding to the ring A, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1, or Partial Structural Formula (C) that are described in any one of Aspects [1-13], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13], [1-14], and [1-15], and subordinate Aspects thereof.

[1-16-1] The compound of Formula (I)-1 according to Aspect [1-16] is preferably a compound in which the ring A is Formula (A), that is, a compound of Formula (II):



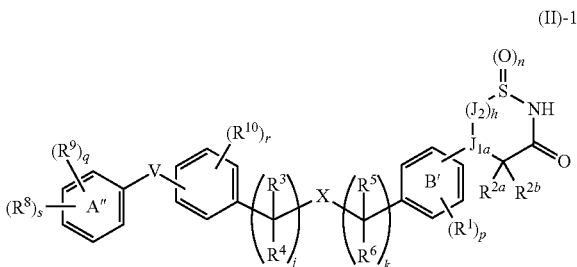
(where n, p, h, j, k, X, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I) described in Aspect [1]; the ring B' and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) described in Aspect [1-13-c] (with the proviso that a compound in which the saturated cyclic amide structure having —S(O)_n—NH—CO— is 1,1-dioxo-1,2-thiazolidin-3-one, the ring B' is a ben-

89

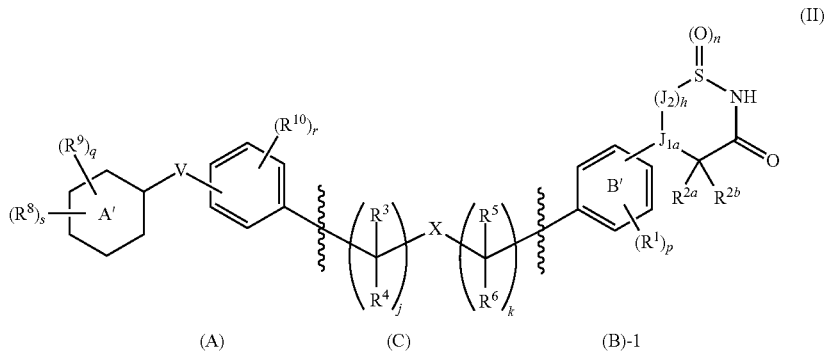
zene ring, k is 1, and in the ring B', the linker moiety containing X and the cyclic amide structure are at the p-position is excluded)).

More specifically, the preferable aspects of n, p, q, r, s, h, j, k, the ring A', the ring B', X, V, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, and R¹⁰ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II) corresponding to Partial Structural Formula (A), Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

The compound of Formula (II) is preferably a compound of Formula (II) in which the ring A' is a benzene ring, a pyridine ring, or a pyrimidine ring, that is, a compound in which the ring A is Formula (A)-1 in Formula (I), which is a compound of Formula (II)-1:



(II)-1



(II)

(where n, p, h, j, k, X, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I) described in Aspect [1]; the ring B' and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c] (with the proviso that a compound in which the saturated cyclic amide structure having —S(O)_n—NH—CO— is 1,1-dioxo-1,2-thiazolidin-3-one, the ring B' is a benzene ring, k is 1, and in the ring B', the linker moiety containing X and the cyclic amide structure are at the p-position is excluded)).

More specifically, the preferable aspects of n, p, q, r, s, h, j, k, the ring A'', the ring B', X, V, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, and R¹⁰ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and the subordinate Aspects thereof. The preferable aspects of the partial

90

structure of Formula (II)-1 corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and the subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

In Formula (II) or Formula (II)-1, X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (II) or Formula (II)-1, j is preferably 1. k is preferably 0. In Formula (II) or Formula (II)-1, more preferably, X is an oxygen atom and k is 0. Further preferably, X is an oxygen atom, j is 1, and k is 0.

In Formula (II) or Formula (II)-1, in the ring B', the linker moiety containing X and the cyclic amide structure are preferably at the p-position, that is, the partial structure has preferably Formula (B1). The ring B' is preferably a benzene ring.

In Formula (II) or Formula (II)-1, preferably, any one of q and s is 1 or more, more preferably, s is 1.

In Formula (II) or Formula (II)-1, preferably, X is an oxygen atom, k is 0, and any one of q and s is 1 or more, more preferably, X is an oxygen atom, k is 0, and s is 1.

[1-16-1a] In the compound of Formula (II), compounds produced by optionally combining the groups of Partial Structural Formula (A) (on the left of the left wavy line), Partial Structural Formula (B) (on the right of the right wavy line), Partial Structural Formula (C) (between the two wavy lines) in Formula (II) can be produced optionally.

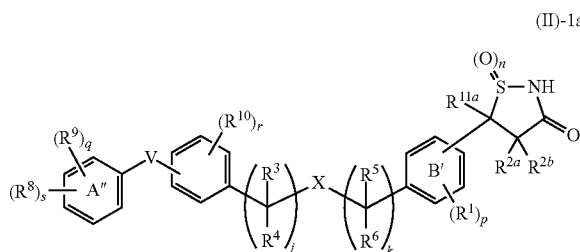
More specifically, Partial Structural Formula (A) is a group optionally selected from Formula (A)-1, Formula (A1), Formula (A2), Formula (A1)-1, Formula (A2)-1, Formula (A1a), Formula (A1b), Formula (A1c), Formula (A1)-1-1, and Formula (A1)-1-2 described in Aspects [1-13-c] to [1-13-c-12]. Partial Structural Formula (B)-1 is a group optionally selected from Formula (B1), Formula (B2), Formula (B1a), and Formula (B1b) described in Aspects [1-14-a-2] and [1-14-a-4], and Partial Structural Formula (C) can be a group optionally selected from Formula (c1) to Formula (c6) described in Aspect [1-15]. An optional combination of each formula forms part of the compound of Formula (I) according to the present invention.

In the compound of Formula (II), preferably, Partial Structural Formula (A) is Formula (A2)-1 in which the ring A''—O— is bonded at 3-position, Formula (A1a), Formula

91

(A1b), or Formula (A1c), Partial Structural Formula (B)-1 is Formula (B1a) or Formula (B1b), and Partial Structural Formula (C) is Formula (c2) or Formula (c5). More preferably, Partial Structural Formula (A) is Formula (A2)-1 in which the ring A''-O— is bonded at 3-position, Formula (A1a), or Formula (A1c), Partial Structural Formula (B)-1 is Formula (B1a), and Partial Structural Formula (C) is Formula (c2). Further preferably, Partial Structural Formula (B-Het)-1 in Partial Structural Formula (B)-1 is Formula (B-Het)-1a, Formula (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, or Formula (B-Het)-1f described in Aspect [1-14-e-1]. An optional combination of each formula forms part of the preferable compound of Formula (I) according to the present invention.

[1-16-1-a] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1a:



(where n, p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, and R^{11a} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c] (with the proviso that a compound in which the saturated cyclic amide structure having —S(O)_n—NH—CO— is 1,1-dioxo-1,2-thiazolidin-3-one, the ring B' is a benzene ring, k is 1, and in the ring B', the linker moiety containing X and the cyclic amide structure are at the p-position is excluded)), a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of n, p, q, r, s, j, k, the ring A'', the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R^{11a} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1a corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1a, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

In Formula (II)-1a, X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (II)-1a, j is preferably 1. k is preferably 0. In Formula (II)-1a, more preferably, x is an oxygen atom and k is 0. Further preferably, X is an oxygen atom, j is 1, and k is 0.

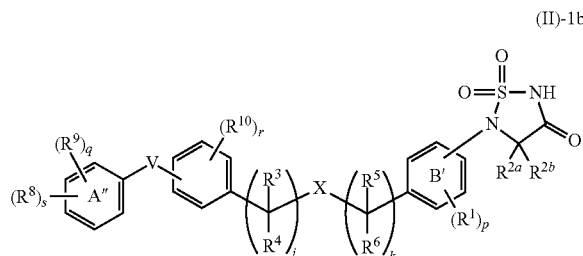
In Formula (II)-1a, in the ring B', the linker moiety containing X and the cyclic amide structure are preferably at the p-position. The ring B' is preferably a benzene ring.

In Formula (II)-1a, preferably, any one of q and s is 1 or more, and more preferably, is 1.

In Formula (II)-1a, preferably, X is an oxygen atom, k is 0, and any one of q and s is 1 or more, and more preferably, X is an oxygen atom, k is 0, and s is 1.

92

[1-16-1-b] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1b:



(where n, p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I) described in Aspect [1]; the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]), or a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of p, q, r, s, j, k, the ring A'', the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, and R¹⁰ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1b corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1b, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

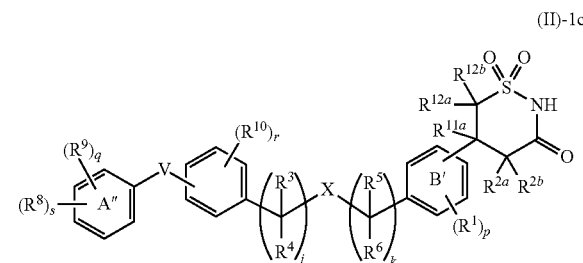
In Formula (II)-1b, X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (II)-1b, j is preferably 1. k is preferably 0. In Formula (II)-1b, more preferably, X is an oxygen atom and k is 0. Further preferably, X is an oxygen atom, j is 1, and k is 0.

In Formula (II)-1b, in the ring B', the linker moiety containing X and the cyclic amide structure are preferably at the p-position. The ring B' is preferably a benzene ring.

In Formula (II)-1b, preferably, any one of q and s is 1 or more, and more preferably, is 1.

In Formula (II)-1b, preferably, X is an oxygen atom, k is 0, and any one of q and s is 1 or more, and more preferably, X is an oxygen atom, k is 0, and s is 1.

[1-16-1-c] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1c:



(where p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R^{11a}, R^{12a}, and R^{12b} are the same as defined in Formula (I); the ring B' is

93

the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]), a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of p, q, r, s, j, k, the ring A'', the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R^{11a}, R^{12a}, and R^{12b} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1c corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1c, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

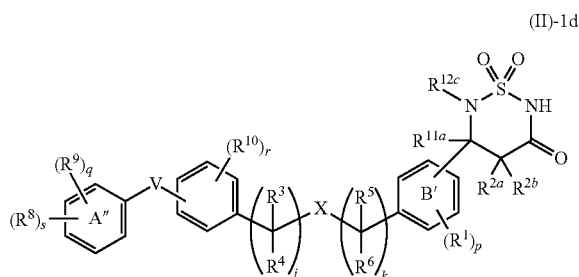
In Formula (II)-1c, X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (II)-1c, j is preferably 1. k is preferably 0. In Formula (II)-1c, more preferably, x is an oxygen atom and k is 0. Further preferably, X is an oxygen atom, j is 1, and k is 0.

In Formula (II)-1c, in the ring B', the linker moiety containing X and the cyclic amide structure are preferably at the p-position. The ring B' is preferably a benzene ring.

In Formula (II)-1c, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II)-1c, preferably, X is an oxygen atom, k is 0, and any one of q and s is 1 or more, and more preferably, X is an oxygen atom, k is 0, and s is 1.

[1-16-1-d] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1d:



(where p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R^{11a} and R^{12c} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]), a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of p, q, r, s, j, k, the ring A'', the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R^{11a}, and R^{12c} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1d corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1d, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

In Formula (II)-1d, X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (II)-1d, j is preferably 1. k is preferably 0. In Formula (II)-1d,

94

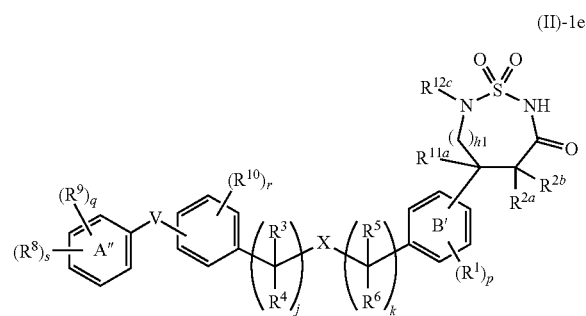
more preferably, x is an oxygen atom and k is 0. Further preferably, X is an oxygen atom, j is 1, and k is 0.

In Formula (II)-1d, in the ring B', the linker moiety containing X and the cyclic amide structure are preferably at the p-position. The ring B' is preferably a benzene ring.

In Formula (II)-1d, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II)-1d, preferably, x is an oxygen atom, k is 0, and any one of q and s is 1 or more, and more preferably, X is an oxygen atom, k is 0, and s is 1.

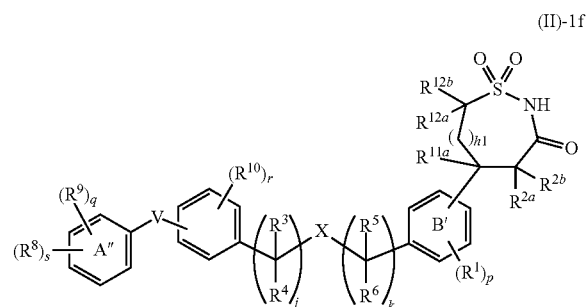
[1-16-1-e] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1e:



(where p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R^{11a}, and R^{12c} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A'', V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; and h1 is the same as defined in Formula (B-Het)-1e described in Aspect [1-14-d]), a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of p, q, r, s, j, k, the ring A'', the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R^{11a}, R^{12c}, and h1 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1e corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1e, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

[1-16-1-f] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably a compound of Formula (II)-1f:

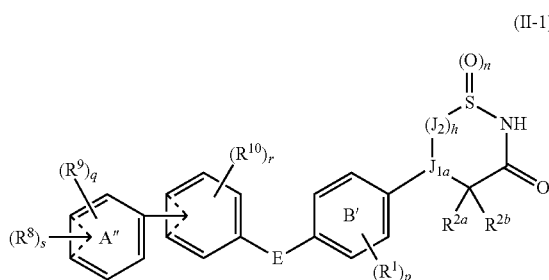


(where p, j, k, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R^{11a}, R^{12a}, and R^{12b} are the same as defined in Formula (I); the ring B' is

the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", V, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; and h1 is the same as defined in Formula (B-Het)-1f described in Aspect [1-14-d]), a salt of the compound, or a solvate of the compound or the salt.

More specifically, the preferable aspects of p, q, r, s, j, k, the ring A", the ring B', X, V, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R^{11a}, R^{12a}, R^{12b}, and h1 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1f corresponding to Partial Structural Formula (A)-1, Partial Structural Formula (B)-1, Partial Structural Formula (B-Het)-1f, or Partial Structural Formula (C) described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c], [1-14], and [1-15], and subordinate Aspects thereof.

[1-16-1-1] The compound of Formula (II) or Formula (II)-1 according to Aspect [1-16-1] is preferably Formula (II)-1-1:



(where n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I); the ring B' and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, the preferable aspects of n, p, q, r, s, h, the ring A", the ring B', J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1 corresponding to Partial Structural Formula (A)-1 or Partial Structural Formula (B1) described in any one of Aspects [1-13-c-1] and [1-14-a-2] are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

In Formula (II)-1, E is preferably Formula (c2) or Formula (c5), more preferably Formula (c2).

In Formula (II)-1, the ring B' is preferably a benzene ring.

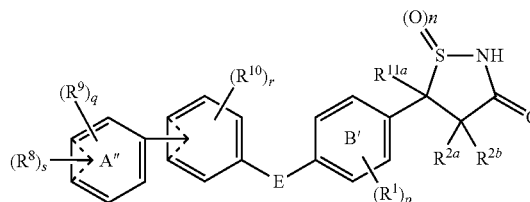
In Formula (II)-1, E and the ring A" are preferably at the m-position.

In Formula (II)-1, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II)-1, preferably, E is Formula (c2), any one of q and s is 1 or more, and more preferably, E is Formula (c2) and s is 1.

[1-16-1-1-a] The compound of Formula (II)-1 is more preferably Formula (II)-1a:

(II)-1a



(where n, p, R¹, R^{2a}, R^{2b}, and R^{11a} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, the preferable aspects of n, p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, R^{11a}, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II)-1a corresponding to Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1a described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

In Formula (II)-1a, E is preferably Formula (c2) or Formula (c5), more preferably Formula (c2).

In Formula (II)-1a, the ring B' is preferably a benzene ring.

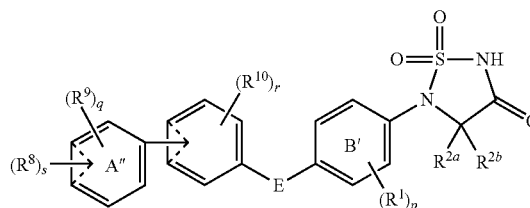
In Formula (II)-1a, E and the ring A" are preferably at the m-position.

In Formula (II)-1a, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II)-1a, preferably, E is Formula (c2), any one of q and s is 1 or more, and more preferably, E is Formula (c2) and s is 1.

[1-16-1-1-b] The compound of Formula (II)-1 is more preferably Formula (II)-1b:

(II)-1b



(where p, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

97

More specifically, the preferable aspects of p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II-1)-1b corresponding to Partial Structural Formula (A1)-1, Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1b described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

In Formula (II-1)-1b, E is preferably Formula (c2) or Formula (c5), more preferably Formula (c2).

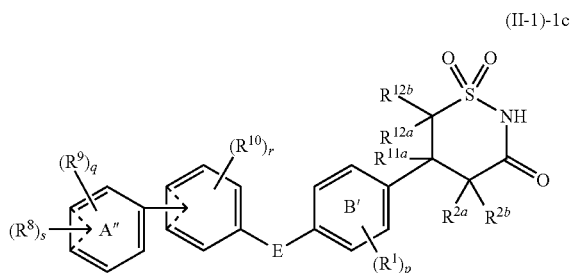
In Formula (II-1)-1b, the ring B' is preferably a benzene ring.

In Formula (II-1)-1b, E and the ring A" are preferably at the m-position.

In Formula (II-1)-1b, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II-1)-1b, preferably, E is Formula (c2), any one of q and s is 1 or more, and more preferably, E is Formula (c2) and s is 1.

[1-16-1-1-c] The compound of Formula (II-1)-1 is more preferably Formula (II-1)-1c:



(where p, R¹, R^{2a}, R^{2b}, R^{11a}, R^{12a}, and R^{12b} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, the preferable aspects of p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, R^{11a}, R^{12a}, R^{12b}, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II-1)-1c corresponding to Partial Structural Formula (A1)-1, Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1c described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

In Formula (II-1)-1c, E is preferably Formula (c2) or Formula (c5), more preferably Formula (c2).

In Formula (II-1)-1c, the ring B' is preferably a benzene ring.

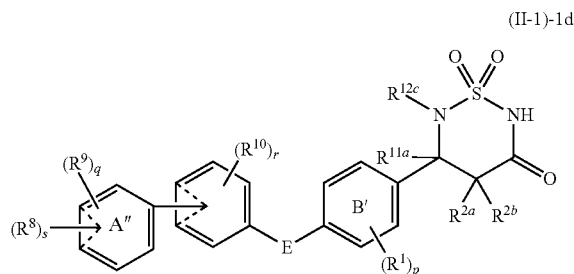
In Formula (II-1)-1c, E and the ring A" are preferably at the m-position.

In Formula (II-1)-1c, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II-1)-1c, preferably, E is Formula (c2), any one of q and s is 1 or more, and more preferably, E is Formula (c2) and s is 1.

98

[1-16-1-1-d] The compound of Formula (II-1)-1 is more preferably Formula (II-1)-1d:



(where p, R¹, R^{2a}, R^{2b}, R^{11a}, and R^{12c} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, the preferable aspects of p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, R^{11a}, R^{12c}, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. The preferable aspects of the partial structure of Formula (II-1)-1d corresponding to Partial Structural Formula (A1)-1, Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1d described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

In Formula (II-1)-1d, E is preferably Formula (c2) or Formula (c5), more preferably Formula (c2).

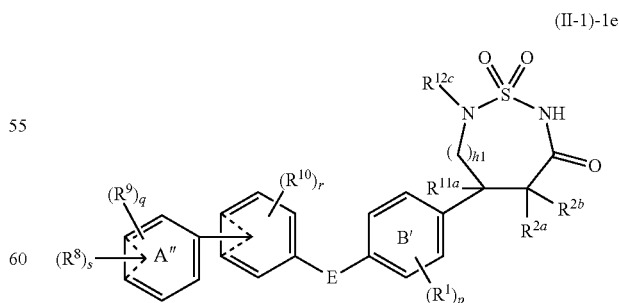
In Formula (II-1)-1d, the ring B' is preferably a benzene ring.

In Formula (II-1)-1d, E and the ring A" are preferably at the m-position.

In Formula (II-1)-1d, preferably, any one of q and s is 1 or more, and more preferably, s is 1.

In Formula (II-1)-1d, preferably, E is Formula (c2), any one of q and s is 1 or more, and more preferably, E is Formula (c2) and s is 1.

[1-16-1-1-e] The compound of Formula (II-1)-1 is more preferably Formula (II-1)-1e:

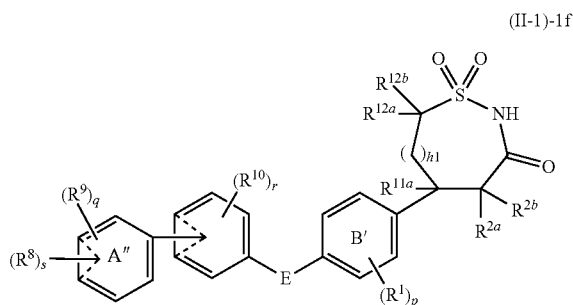


(where p, R¹, R^{2a}, R^{2b}, R^{11a}, and R^{12c} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or

Formula (A)-1 described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1e described in Aspect [1-14-d]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, preferable aspects of p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, R^{11a}, R^{12c}, h1, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1)-1e corresponding to Partial Structural Formula (A 1)-1, Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1e described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

[1-16-1-1-f] The compound of Formula (II-1)-1 is more preferably Formula (II-1)-1f:

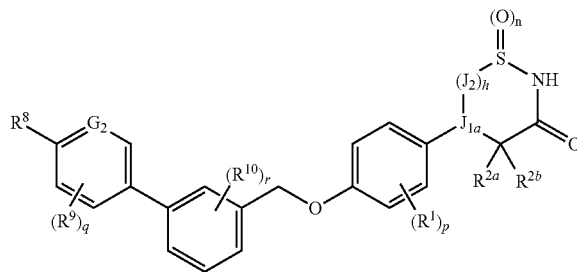


(where p, R¹, R^{2a}, R^{2b}, R^{11a}, R^{12a}, and R^{12b} are the same as defined in Formula (I); the ring B' is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, s, the ring A", R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1f described in Aspect [1-14-d]; the broken lines are the same as defined in Formula (A1)-1 described in Aspect [1-13-c-1]; and E is a group optionally selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, preferable aspects of p, q, r, s, the ring A", the ring B', R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, R^{11a}, R^{12a}, R^{12b}, h1, the broken lines, and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1)-1f corresponding to Partial Structural Formula (A1)-1, Partial Structural Formula (B1), or Partial Structural Formula (B-Het)-1f described in any one of Aspects [1-13-c-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

[1-16-1-2] The compound of Formula (II-1)-1 according to Aspect [1-16-1-1] is more preferably Formula (II-1-A):

(II-1-A)



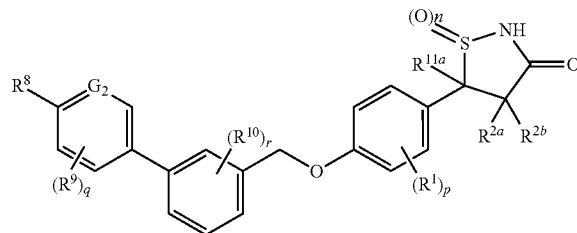
(where n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I); J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, r, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) described in Aspect [1-13-c]; and G₂ is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of n, p, q, r, h, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹⁰, and G₂ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A) corresponding to Partial Structural Formula (A1a) or Partial Structural Formula (B1a) described in Aspect [1-13-c-3-1] or [1-14-a-4] are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

[1-16-1-2a] In Formula (II-1-A), preferably, r is 0 or 1 and R¹⁰ is a C₁₋₄ alkyl group. Preferably, q is an integer of 1 to 3 and R⁹ is a halogen atom or a C₁₋₄ alkyl group. R⁸ is preferably a C₁₋₆ alkoxy group (the alkoxy group is substituted with 1 to 5 —OH, 1 to 5 ethoxy, 1 to 5 methylsulfonyl, 1 to 5 sulfamoyl, 1 to 5 methylsulfamoyl, 1 to 5 dimethylsulfamoyl, 1 to 5 carbamoyl, 1 to 5 methylcarbamoyl, 1 to 5 dimethylcarbamoyl, 1 to 5 —NH₂, 1 to 5 acetylamino, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, or 1 to 5 3-methyloxetane-3-yl) or (1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy. More preferably, R⁸ is a C₁₋₆ alkoxy group (the alkoxy group is substituted with 1 to 5 —OH, 1 to 5 ethoxy, 1 to 5 methylsulfonyl, 1 to 5 —NH₂, 1 to 5 acetylamino, 1 to 5 methylsulfonylamino, 1 to 5 2-oxo-1-pyrrolidinyl, or 1 to 5 3-methyloxetane-3-yl) or (1,1-dioxidetetrahydro-2H-thiopyran-4-yl)oxy. Further preferably, R⁸ is a C₁₋₆ alkoxy group (the alkoxy group is substituted with 1 to 2 —OH, 1 to 2 ethoxy, 1 to 2 methylsulfonyl, or 1 to 2 —NH₂).

[1-16-1-2-a] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-a:

(II-1-A)-a

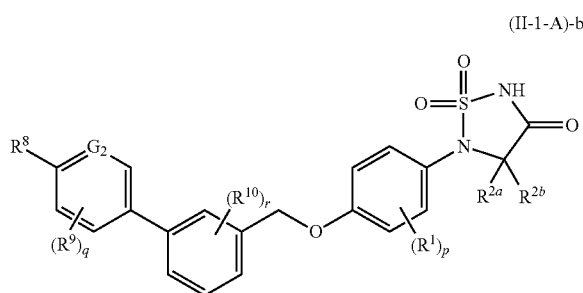


(where n, p, R¹, R^{2a}, R^{2b}, and R^{11a} are the same as defined in Formula (I); q, r, R⁸, R⁹, and R¹⁰ are the same as defined in Formula (A) described in Aspect [1-13-c]; and G₂ is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

101

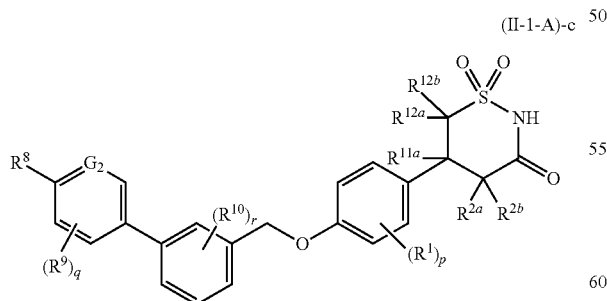
More specifically, preferable aspects of n, p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , R^{11a} and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-a corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1a described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

[1-16-1-2-b] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-b:



(where p, R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); q, r, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]). More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-b corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1b described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

[1-16-1-2-c] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-c:

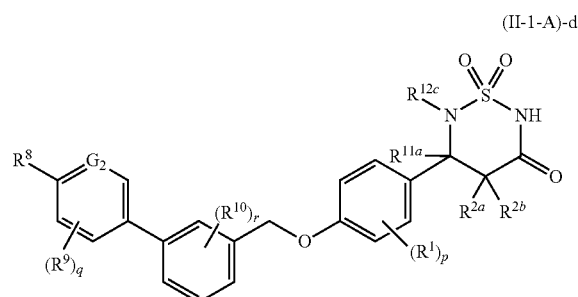


(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , R^{12a} , and R^{12b} are the same as defined in Formula (I); q, r, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

102

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , R^{11a} , R^{12a} , R^{12b} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-c corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1c described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

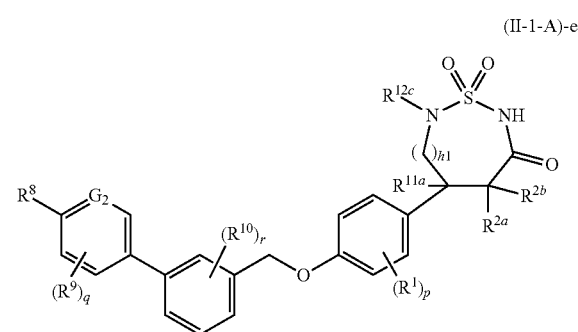
[1-16-1-2-d] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-d:



(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , and R^{12c} are the same as defined in Formula (I); q, r, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , R^{11a} , R^{12c} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-d corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1d described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

[1-16-1-2-e] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-e:



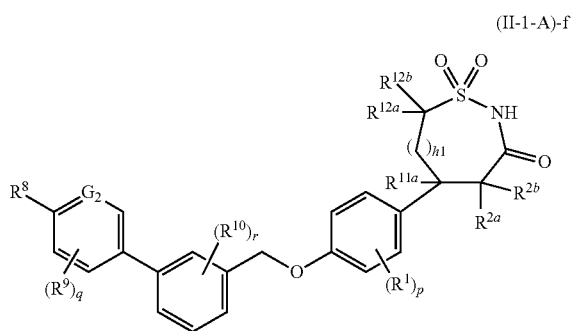
(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , and R^{12c} are the same as defined in Formula (I); q, r, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1e described in Aspect [1-13-c-3-1]).

103

[1-14-d]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , R^{11a} , R^{12c} , h1, and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-e corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1e described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

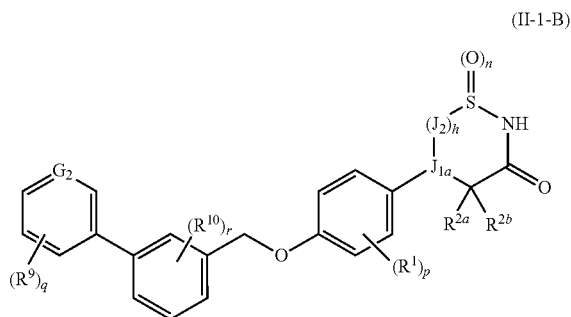
[1-16-1-2-f] The compound of Formula (II-1-A) according to Aspect [1-16-1-2] is more preferably Formula (II-1-A)-f:



(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , R^{12a} , and R^{12b} are the same as defined in Formula (I); q, r, R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1f described in Aspect [1-14-d]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , R^{11a} , R^{12a} , R^{12b} , h1, and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-A)-f corresponding to Partial Structural Formula (A1a), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1f described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^8 , R^9 , and R^{10} are the same as described in Aspect [1-16-1-2a].

[1-16-1-3] The compound of Formula (II-1)-1 according to Aspect [1-16-1-1] is more preferably Formula (II-1-B):



(where n, p, h, J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); J_{1a} is the same as defined in Formula (B)-1

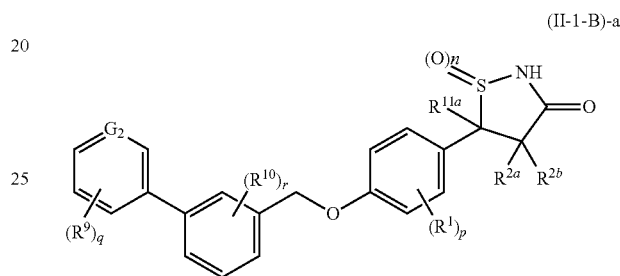
104

described in Aspect [1-14-a-1]; q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

Specifically, preferable aspects of n, p, q, r, h, J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B) corresponding to Partial Structural Formula (A1c) or Partial Structural Formula (B1a) described in Aspect [1-13-c-3-1] or [1-14-a-4] are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof.

[1-16-1-3a] In Formula (II-1-B), preferably, r is 0 or 1 and R^{10} is a C_{1-4} alkyl group. Preferably, q is an integer of 1 to 3 and R^9 is a halogen atom or a C_{1-4} alkyl group.

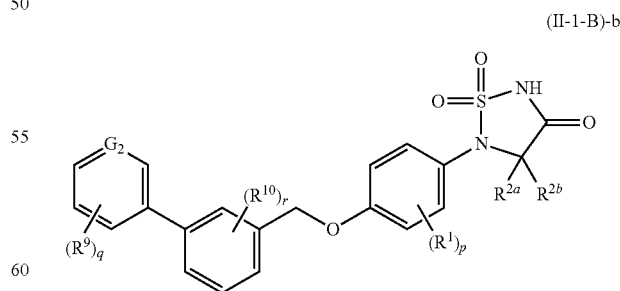
[1-16-1-3-a] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-a:



(where n, p, R^1 , R^{2a} , R^{2b} , and R^{11a} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of n, p, q, r, R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , R^{11a} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-a corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1a described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^9 , and R^{10} are the same as described in Aspect [1-16-1-3a].

[1-16-1-3-b] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-b:

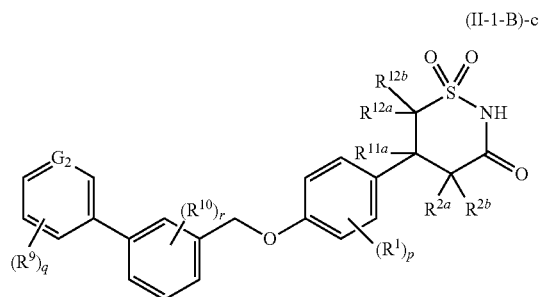


(where p, R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

105

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-b corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1b described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^9 , and R^{10} are the same as described in Aspect [1-16-1-3a].

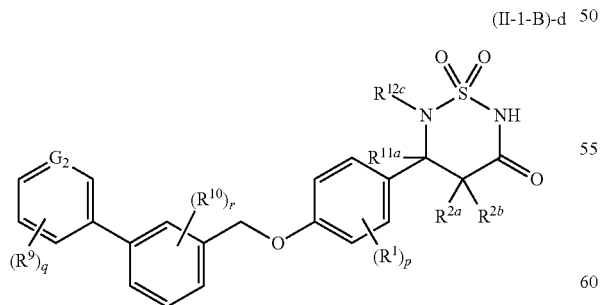
[1-16-1-3-c] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-c:



(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , R^{12a} , and R^{12b} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , R^{11a} , R^{12a} , R^{12b} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-c corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1c described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^9 , and R^{10} are the same as described in Aspect [1-16-1-3a].

[1-16-1-3-d] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-d:

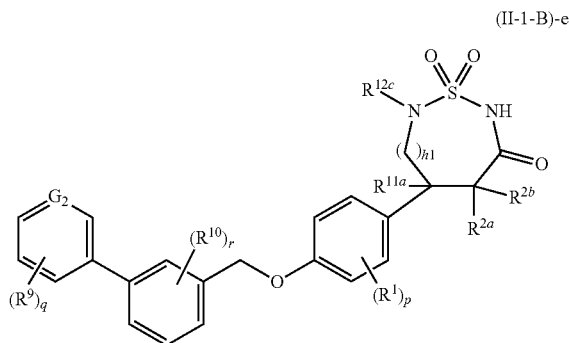


(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , and R^{12c} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

106

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , R^{11a} , R^{12c} , and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-d corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1d described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^9 , and R^{10} are the same as described in Aspect [1-16-1-3a].

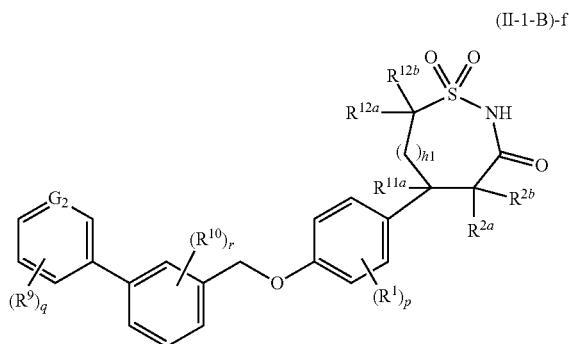
[1-16-1-3-e] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-e:



(where p, R^{2a} , R^{2b} , R^{11a} , and R^{12c} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1e described in Aspect [1-14-d]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R^1 , R^{2a} , R^{2b} , R^9 , R^{10} , R^{11a} , R^{12c} , h1, and G_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-e corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1e described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R^9 , and R^{10} are the same as described in Aspect [1-16-1-3a].

[1-16-1-3-f] The compound of Formula (II-1-B) according to Aspect [1-16-1-3] is more preferably Formula (II-1-B)-f:



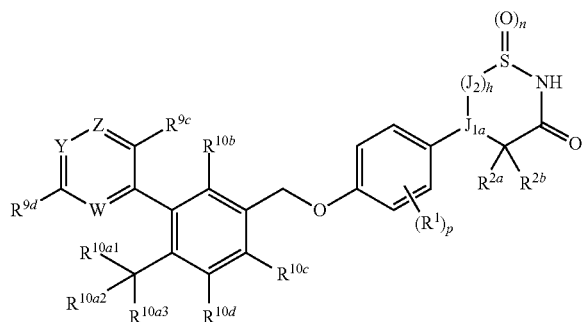
(where p, R^1 , R^{2a} , R^{2b} , R^{11a} , R^{12a} , and R^{12b} are the same as defined in Formula (I); q, r, R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and G_2 is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

107

defined in Formula (A) described in Aspect [1-13-c]; h1 is the same as defined in Formula (B-Het)-1f described in Aspect [1-14-d]; and G₂ is the same as defined in Formula (A1a) described in Aspect [1-13-c-3-1]).

More specifically, preferable aspects of p, q, r, R¹, R^{2a}, R^{2b}, R⁹, R¹⁰, R^{11a}, R^{12a}, R^{12b}, h1, and G₂ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of the partial structure of Formula (II-1-B)-f corresponding to Partial Structural Formula (A1c), Partial Structural Formula (B1a), or Partial Structural Formula (B-Het)-1f described in any one of Aspects [1-13-c-3-1] and [1-14], and subordinate Aspects thereof are the same as described in any one of Aspects [1-13-c] and [1-14], and subordinate Aspects thereof. Preferable aspects of q, r, R⁹, and R¹⁰ are the same as described in Aspect [1-16-1-3a].

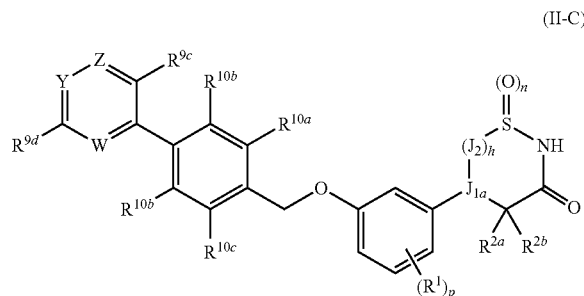
[1-16-1-4] As the compound of Formula (I) according to Aspect [1] or of Formula (II) or Formula (II)-1 according to Aspect [1-16-1], a preferable compound is Formula (II-B):



(where n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and W, Y, Z, R^{9c}, R^{9d}, R^{10a1}, R^{10a2}, R^{10a3}, R^{10b}, R^{10c}, and R^{10d} are the same as defined in Formula (A1)-1-1 or Formula (R^{10a'}) described in Aspect [1-13-c-11]).

More specifically, preferable aspects of n, p, h, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, W, Y, Z, R^{9c}, R^{9d}, R^{10a1}, R^{10a2}, R^{10a3}, R^{10b}, R^{10c}, and R^{10d} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

[1-16-1-5] As the compound of Formula (I) according to Aspect [1] or of Formula (II) or Formula (II)-1 according to Aspect [1-16-1], a preferable compound is Formula (II-C):



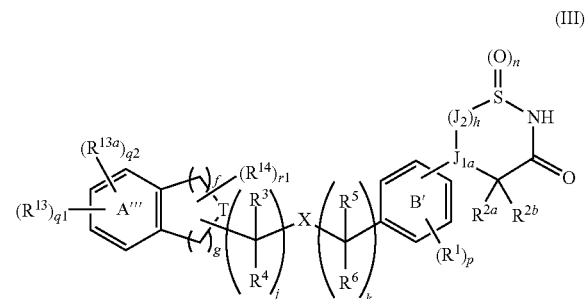
(where n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as

108

defined in Formula (B)-1 described in Aspect [1-14-a-1]; and W, Y, Z, R^{9c}, R^{9d}, R^{10a}, R^{10b}, R^{10c}, and R^{10d} are the same as defined in Formula (A1)-1-1 described in Aspect [1-13-c-11]).

More specifically, preferable aspects of n, p, h, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, W, Y, Z, R^{9c}, R^{9d}, R^{10a}, R^{10b}, R^{10c}, and R^{10d} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

[1-16-2] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (AA), that is, a compound of Formula (III):



(where n, p, h, j, k, J₂, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, and R⁶ are the same as defined in Formula (I); the ring B' and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and f, g, q1, q2, r1, the ring A'', T, R¹³, R^{13a}, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]), a salt of the compound, or a solvate of the compound or the salt.

More specifically, preferable aspects of n, p, h, j, k, f, g, q1, q2, r1, the ring A'', the ring B', J_{1a}, J₂, T, X, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R¹³, R^{13a}, and R¹⁴ are the same as described in any one of Aspects [1-1] to [1-15] and the subordinate Aspects thereof.

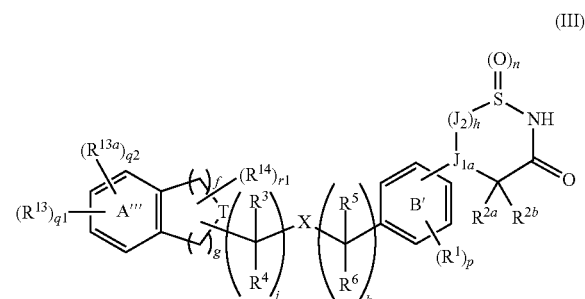
In Formula (III), X is preferably an oxygen atom or —NH—, more preferably an oxygen atom. In Formula (III), j is preferably 0, and k is preferably 0. In Formula (III), more preferably, X is an oxygen atom, j is 0, and k is 0.

In Formula (III), the ring B' is preferably a benzene ring.

In Formula (III), preferably, any one of q1 and q2 is 1 or more and more preferably, q2 is 1.

In Formula (III), preferably, X is an oxygen atom, j is 0, k is 0, and any one of q1 and q2 is 1 or more, and more preferably, X is an oxygen atom, j is 0, k is 0, and q2 is 1.

When the definitions of the substituents are assembled once more and are described in detail, Aspect [1-16-2] is a compound of Formula (III):



(where n is an integer of 0 to 2; p is an integer of 0 to 4; h is an integer of 0 to 3; j is an integer of 0 to 3; k is an integer of 0 to 2;
 J_{1a} is $-\text{CR}^{1a}$ or a nitrogen atom; J_2 is $-\text{CR}^{12a}\text{R}^{12b}$ or $-\text{NR}^{12c}$ (with the proviso that when J_{1a} is a nitrogen atom, h is 0);
 X is an oxygen atom, a sulfur atom, or $-\text{NR}^7$;
 the ring B' is a benzene ring, a pyridine ring, or a pyrimidine ring;
 f is an integer of 0 to 2; g is an integer of 1 to 4; q1 is an integer of 0 to 3; q2 is 0 or 1; r1 is an integer of 0 to 2 (with the proviso that $q1+q2+r1$ is an integer of 0 to 5);
 the ring A''' is a benzene ring or a pyridine ring;
 T is a group optionally selected from $-\text{CH}_2-$, an oxygen atom, $-\text{S}(\text{O})_i$ (i is an integer of 0 to 2), and a $-\text{NR}^7$ group;
 R^1 's are independently a group optionally selected from a halogen atom, a C_{1-6} alkyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkenyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkynyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{1-6} alkoxy group that is optionally substituted with 1 to 5 substituent(s) RI, and a cyano group; R^{2a} and R^{2b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkoxy group, and a cyano group;
 R^3 , R^4 , R^5 , R^6 , and R^7 are independently a group optionally selected from a hydrogen atom, a C_{1-6} alkyl group, a halogenated C_{1-6} alkyl group, a C_{2-6} alkenyl group, and a C_{2-6} alkynyl group;
 R^{11a} 's are independently a group optionally selected from a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halogenated C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkoxy group, a halogenated C_{1-6} alkoxy group, a C_{2-7} alkanoyl group, and a carboxy group that is optionally protected;
 R^{12a} and R^{12b} are independently a group optionally selected from a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a halogenated C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkoxy group, a halogenated C_{1-6} alkoxy group, and a cyano group;
 R^{12c} 's are independently a group optionally selected from a hydrogen atom, a C_{1-6} alkyl group, and a halogenated C_{1-6} alkyl group;
 R^{13} 's are independently a group optionally selected from a halogen atom, $-\text{OH}$, a cyano group, a C_{1-10} alkyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkenyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkynyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{1-10} alkoxy group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkenyloxy group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-10} alkynyloxy group that is optionally substituted with 1 to 5 substituent(s) RI, $-\text{SH}$, a $-\text{S}(\text{O})_i\text{R}^a$ (i is an integer of 0 to 2) group, and a $-\text{NR}^b\text{R}^c$ group;
 R^{13a} is a group optionally selected from an aryl group that is optionally substituted with 1 to 5 substituent(s) RII, a heterocyclic group that is optionally substituted with 1 to 5 substituent(s) RII, an aralkyl group that is optionally substituted with 1 to 5 substituent(s) RII, a heteroarylalkyl group that is optionally substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic alkyl group that is optionally substituted with 1 to 5 substituent(s) RII, an aryloxy group that is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group that is optionally

substituted with 1 to 5 substituent(s) RII, a non-aromatic heterocyclic oxy group that is optionally substituted with 1 to 5 substituent(s) RII, an aralkyloxy group that is optionally substituted with 1 to 5 substituent(s) RII, a heteroaryloxy group that is optionally substituted with 1 to 5 substituent(s) RII, and a substituted spiropiperidinylmethyl group;
 R^{14} 's are independently a group optionally selected from a halogen atom, $-\text{OH}$, a cyano group, a C_{1-6} alkyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkenyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{2-6} alkynyl group that is optionally substituted with 1 to 5 substituent(s) RI, a C_{1-6} alkoxy group that is optionally substituted with 1 to 5 substituent(s) RI, $-\text{SH}$, a $-\text{S}(\text{O})_i\text{R}^a$ (i is an integer of 0 to 2) group, and a $-\text{NR}^b\text{R}^c$ group;
 R^a is a C_{1-6} alkyl group or a halogenated C_{1-6} alkyl group;
 R^b and R^c are independently a group optionally selected from a hydrogen atom, a C_{1-6} alkyl group, a halogenated C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{2-7} alkanoyl group (the alkanoyl group is optionally substituted with $-\text{OH}$ or a C_{1-6} alkoxy group), a C_{1-6} alkylsulfonyl group, an arylcarbonyl group, and a heterocyclic carbonyl group, where R^b and R^c optionally form together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C_{1-6} alkyl group that is optionally substituted with 1 to 5 substituent(s) RI) or with a carbonyl group, and the cyclic group is further optionally substituted with 1 to 5 substituent(s) RII;
 where the substituents RI may be the same as or different from each other and be each a group optionally selected from a halogen atom, $-\text{OH}$, a cyano group, a C_{1-6} alkoxy group (the C_{1-6} alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 $-\text{OH}$, 1 to 5 C_{1-6} alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 $-\text{S}(\text{O})_i\text{R}^a$ (i is an integer of 0 to 2) group(s), 1 to 5 $-\text{SO}_2\text{NR}^d\text{R}^e$ group(s), 1 to 5 $-\text{CONR}^d\text{R}^e$ group(s), or 1 to 5 $-\text{NR}^{b1}\text{R}^{c1}$ group(s)), a $-\text{NR}^{b1}\text{R}^{c1}$ group, and a heterocyclic oxy group (the heterocyclic oxy group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s));
 the substituents RII may be the same as or different from each other and be each a group optionally selected from the substituents RI, a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 $-\text{OH}$, 1 to 5 C_{1-6} alkoxy group(s), 1 to 5 $-\text{S}(\text{O})_i\text{R}^a$ (i is an integer of 0 to 2) group(s), 1 to 5 $-\text{NR}^{b1}\text{R}^{c1}$ group(s), 1 to 5 $-\text{SO}_2\text{NR}^d\text{R}^e$ group(s), or 1 to 5 $-\text{CONR}^d\text{R}^e$ group(s)), a C_{2-6} alkenyl group, a C_{2-7} alkanoyl group, an aralkyloxy group, a heterocyclic group (the heterocyclic group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s)), a heterocyclic carbonyl group (the heterocyclic carbonyl group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s)), a $-\text{S}(\text{O})_i\text{R}^a$ (i is an integer of 0 to 2) group, a $-\text{CONR}^d\text{R}^e$ group, and a $-\text{CONR}^d\text{R}^{e1}$ group;
 R^d and R^e are independently a hydrogen atom or a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 $-\text{OH}$, or 1 to 5 C_{1-6} alkoxy group(s));

111

R^{e1} is a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 $-OH$, 1 to 5 C_{1-6} alkoxy group(s), 1 to 5 aryl group(s) (the aryl group is optionally substituted with 1 to 3 halogen atom(s)), 1 to 5 heterocyclic group(s) (the heterocyclic group is optionally substituted with 1 to 3 C_{1-6} alkyl group(s) or 1 to 3 oxo group(s)), 1 to 5 $-S(O)_h R^a$ (i is an integer of 0 to 2) group(s), 1 to 5 $-SO_2 NR^d R^e$ group(s), 1 to 5 $-CONR^d R^e$ group(s), or 1 to 5 $-NR^{b1} R^{c1}$ group(s)); and

R^{b1} and R^{c1} are independently a group optionally selected from a hydrogen atom, a C_{1-6} alkyl group, a C_{2-7} alkanoyl group, and a C_{1-6} alkylsulfonyl group, where R^{b1} and R^{c1} optionally form together with a nitrogen atom to which they are bonded, a 3- to 8-membered cyclic group, where in the cyclic group, one or two carbon atom(s) is(are) optionally substituted with an atom optionally selected from an oxygen atom, a sulfur atom, and a nitrogen atom (the nitrogen atom is optionally substituted with a C_{1-6} alkyl group) or with a carbonyl group), a salt of the compound, or a solvate of the compound or the salt.

[1-16-2-0] In the compound of Formula (III) according to Aspect [1-16-2], J_{1a} and h are preferably in such a relationship that when J_{1a} is a nitrogen atom, h is 0 and when J_{1a} is CR^{11a} , h is an integer of 0 to 1.

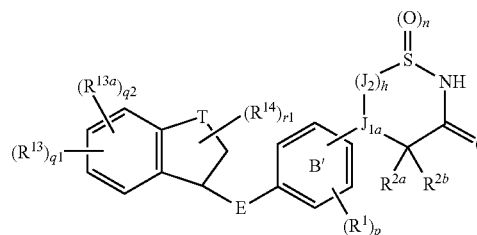
[1-16-2a] In the compound of Formula (III) according to Aspect [1-16-2], compounds produced by optionally combining the groups of Partial Structural Formula (AA) (on the left of the left wavy line), Partial Structural Formula (B)-1 (on the right of the right wavy line), and Partial Structural Formula (C) (between the two wavy lines) in Formula (III):

112

Formula (B-Het)-1f described in Aspect [1-14-e-1]. In Formula (III), a compound having Formula (B-Het)-1a is Formula (III)-1a, a compound having Formula (B-Het)-1b is Formula (III)-1b, a compound having Formula (B-Het)-1c is Formula (III)-1c, a compound having Formula (B-Het)-1d is Formula (III)-1d, a compound having Formula (B-Het)-1e is Formula (III)-1e, and a compound having Formula (B-Het)-1f is Formula (III)-1f.

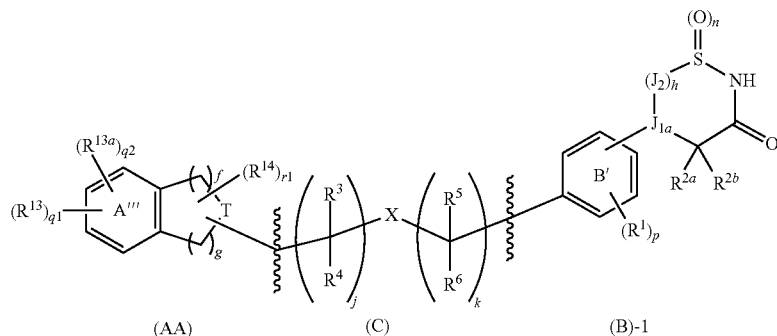
[1-16-2-1] The compound of Formula (III) according to Aspect [1-16-2] is preferably Formula (III)-1:

(III-1)



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); the ring B' and J_{1a} are the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; $q1$, $q2$, $r1$, T , R^{13} , R^{13a} , and R^{14} are the same as defined in Formula (AA) described in Aspect [1-13-d]; and E is a group optionally

(III)



can be produced optionally.

More specifically, Partial Structural Formula (AA) is a group optionally selected from Formula (AA)-1, Formula (AA)-1-1, Formula (AA1), Formula (AA1)-1, Formula (AA1a)-1, Formula (AA1a)-1-1, Formula (AA1b), and Formula (AA1b)-1 described in Aspects [1-13-d-1] to [1-13-d-7-1]. Partial Structural Formula (B) is a group optionally selected from Formula (B1), Formula (B2), Formula (B1a), and Formula (B1b) described in Aspects [1-14-a-2] and [1-14-a-4], and Partial Structural Formula (C) can be a group optionally selected from Formula (c1) to Formula (c6) described in Aspect [1-15]. An optional combination of each formula forms part of the compound of Formula (I) according to the present invention.

The cyclic amide structure bonded to the ring B' of Formula (III) is Partial Structural Formula (B-Het)-1 described in Aspect [1-14-e], and preferable examples of the cyclic amide structure include Formula (B-Het)-1a, (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, and

selected from Formula (c1) to Formula (c6) shown as specific examples of Formula (C) described in Aspect [1-15].

More specifically, preferable aspects of n , p , h , $q1$, $q2$, $r1$, the ring B' , T , J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^{13} , R^{13a} , R^{14} , and E are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

In Formula (III-1), E is preferably Formula (c1) or Formula (c4), and more preferably Formula (c1).

In Formula (III-1), the ring B' is preferably a benzene ring.

In Formula (III-1), preferably, any one of $q1$ and $q2$ is 1 or more, and more preferably, $q2$ is 1.

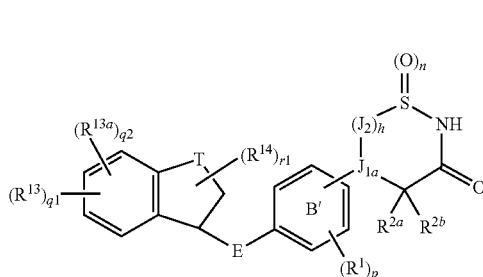
In Formula (III-1), preferably, E is Formula (c1) and any one of $q1$ and $q2$ is 1 or more, and more preferably, E is Formula (c1) and $q2$ is 1.

The cyclic amide structure bonded to the ring B' of Formula (III-1) is Partial Structural Formula (B-Het)-1 described in Aspect [1-14-e], and preferable examples of the cyclic amide structure include Formula (B-Het)-1a, (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, and

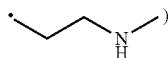
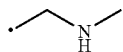
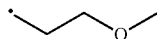
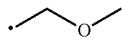
113

Formula (B-Het)-1f described in Aspect [1-14-e-1]. In Formula (III-1), a compound having Formula (B-Het)-1a is Formula (III-1)-1a, a compound having Formula (B-Het)-1b is Formula (III-1)-1b, a compound having Formula (B-Het)-1c is Formula (III-1)-1c, a compound having Formula (B-Het)-1d is Formula (III-1)-1d, a compound having Formula (B-Het)-1e is Formula (III-1)-1e, and a compound having Formula (B-Het)-1f is Formula (III-1)-1f.

When the definitions of the substituents are assembled once more and are described in detail, Aspect [1-16-2-1] is a compound of Formula (III-1):



(where n, p, h, q1, q2, r1, the ring B', T, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R¹³, R^{13a}, and R¹⁴ are the same as defined in Formula (III) according to Aspect [1-16-2]; and E is a group optionally selected from Formula (c1) to Formula (c6):



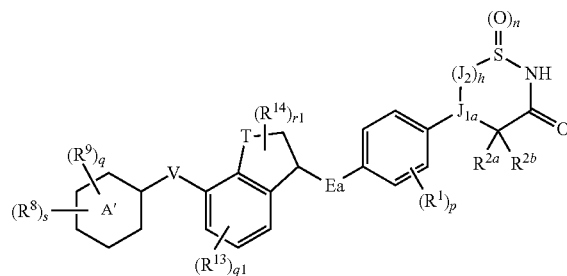
that is a compound of Formula (III) according to Aspect [1-16-2], a salt of the compound, or a solvate of the compound or the salt.

[1-16-2-1-a] In the compound of Formula (III) according to Aspect [1-16-2-1], J_{1a} and h are preferably in such a relationship that when J_{1a} is a nitrogen atom, h is 0 and when J_{1a} is CR^{11a}, h is an integer of 0 to 1.

[1-16-2-2] The compound of Formula (III) according to Aspect [1-16-2] or of Formula (III-1) according to Aspect [1-16-2-1] is preferably Formula (III-1)-1:

114

(III-1)-1



(where n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I); J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, s, the ring A', V, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; q1, r1, T, R¹³, and R¹⁴ are the same as defined in Formula (AA) described in Aspect [1-13-d]; and Ea is Formula (c1) or Formula (c4) shown as specific examples of Formula (C) described in Aspect [1-15]).

More specifically, preferable aspects of n, p, h, q, q1, r1, s, the ring A', V, T, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹³, R¹⁴, and Ea are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

In Formula (III-1)-1, Ea is preferably Formula (c1).

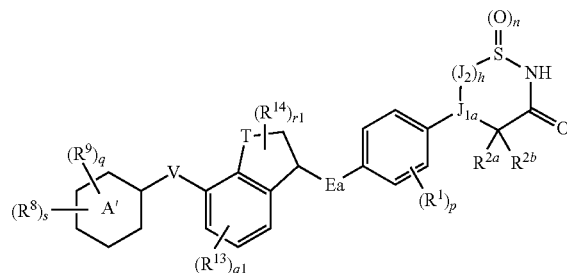
In Formula (III-1)-1, any one of q and s is preferably 1 or more.

In Formula (III-1)-1, more preferably, Ea is Formula (c1) and any one of q and s is 1 or more.

(c1) The cyclic amide structure bonded to the ring B of Formula (III-1)-1 is Partial Structural Formula (B-Het)-1 described in Aspect [1-14-e], and preferable examples of the cyclic amide structure include Formula (B-Het)-1a, (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, and Formula (B-Het)-1f described in Aspect [1-14-e-1]. In Formula (III-1)-1, a compound having Formula (B-Het)-1a is Formula (III-1)-1a, a compound having Formula (B-Het)-1b is Formula (III-1)-1b, a compound having Formula (B-Het)-1c is Formula (III-1)-1c, a compound having Formula (B-Het)-1d is Formula (III-1)-1d, a compound having Formula (B-Het)-1e is Formula (III-1)-1e, and a compound having Formula (B-Het)-1f is Formula (III-1)-1f.

When the definitions of the substituents are assembled once more and are described in detail, Aspect [1-16-2-2] is a compound of Formula (III-1)-1:

(III-1)-1



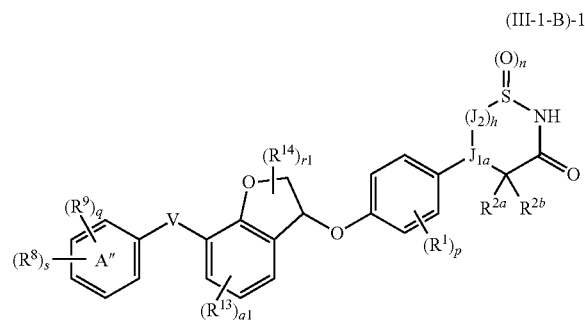
(where n, p, h, T, J₂, R¹, R^{2a}, R^{2b}, and J_{1a} are the same as defined in Formula (III) according to Aspect [1-16-2];

(where n, p, h, q, q1, r1, s, V, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R⁸, R⁹, R¹³, and R¹⁴ are the same as defined in Formula (III-1)-1 according to Aspect [1-16-2-2]; and the ring A" is a benzene ring, a pyridine ring, or a pyrimidine ring) that is a compound of Formula (III-1)-1 according to Aspect [1-16-2-2], a salt of the compound, or a solvate of the compound or the salt.

117

[1-16-2-3-1] In the compound of Formula (III-1-A)-1 according to Aspect [1-16-2-3], J_{1a} and h are preferably in such a relationship that when J_{1a} is a nitrogen atom, h is 0 and when J_{1a} is CR^{11a} , h is an integer of 0 to 1.

[1-16-2-4] The compound of Formula (III-1)-1 according to Aspect [1-16-2-2] is preferably Formula (III-1-B)-1:



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I); J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q , s , the ring A'', V , R^8 , and R^9 are the same as defined in Formula (A) or Formula (A)-1 described in Aspect [1-13-c]; and $q1$, $r1$, R^{13} , and R^{14} are the same as defined in Formula (AA) described in Aspect [1-13-d]).

More specifically, preferable aspects of n , p , h , q , $q1$, $r1$, s , the ring A'', V , J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{13} , and R^{14} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

In Formula (III-1-B)-1, any one of q and s is preferably 1 or more.

The cyclic amide structure bonded to the ring B of Formula (III-1-B)-1 is Partial Structural Formula (B-Het)-1 described in Aspect [1-14-e], and preferable examples of the cyclic amide structure include Formula (B-Het)-1a, (B-Het)-1b, Formula (B-Het)-1c, Formula (B-Het)-1d, Formula (B-Het)-1e, and Formula (B-Het)-1f described in Aspect [1-14-e-1]. In Formula (III-1-B)-1, a compound having Formula (B-Het)-1a is Formula (III-1-B)-1-1a, a compound having Formula (B-Het)-1b is Formula (III-1-B)-1-1b, a compound having Formula (B-Het)-1c is Formula (III-1-B)-1-1c, a compound having Formula (B-Het)-1d is Formula (III-1-B)-1-1d, a compound having Formula (B-Het)-1e is Formula (III-1-B)-1-1e, and a compound having Formula (B-Het)-1f is Formula (III-1-A)-1-1f.

[1-16-2-5] In the compound of Formula (III-1)-1 according to Aspect [1-16-2-2] and in Formula (III-1-A)-1 according to Aspect [1-16-2-3], it is preferred that R^8 's are independently a group optionally selected from a C_{1-6} alkoxy group that is substituted with 1 to 5 substituent(s) M, a $CONR^dR^{e1}$ group, and an aralkyloxy group; the substituents M are independently a group optionally selected from a halogen atom, OH , a C_{1-6} alkoxy group, a $S(O)_iR^a$ (i is an integer of 0 to 2 and R^a is a C_{1-6} alkyl group or a halogenated C_{1-6} alkyl group) group, a $NR^{b1}R^{c1}$ group, a $SO_2NR^dR^e$ group, and a $CONR^dR^e$ group; and R^9 's are independently a group optionally selected from a halogen atom, OH , a cyano group, a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 OH , 1 to 5 C_{1-6} alkoxy group(s), 1 to 5 $S(O)_iR^a$ (i is an integer of 0 to 2 and R^a is a C_{1-6} alkyl group or a halogenated C_{1-6} alkyl group) group(s), or 1 to 5 $NR^{b1}R^{c1}$ group(s)), a C_{2-6} alkenyl group, a C_{1-6} alkoxy group (the C_{1-6} alkoxy group is optionally substituted with 1 to 5 halogen atom(s), 1 to 5 OH , 1 to 5 C_{1-6} alkoxy group(s), or 1 to 5 $NR^{b1}R^{c1}$ group(s)), a C_{2-7} alkanoyl group, a $S(O)_iR^a$ (i is an integer of 0 to 2 and R^a is

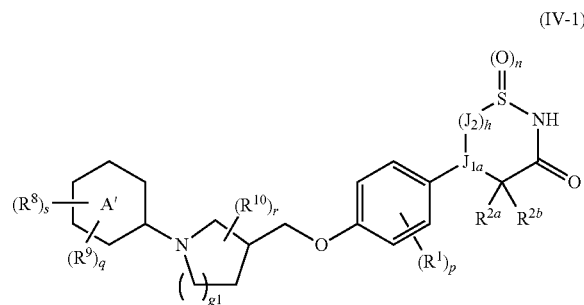
118

a C_{1-6} alkyl group or a halogenated C_{1-6} alkyl group) group, a $NR^{b1}R^{c1}$ group, and a $CONR^dR^e$ group.

[1-16-2-6] In the compound of Formula (III-1)-1, and Formula (III-1-A)-1 that are quoted in [1-16-2-5], it is more preferred that R^8 's are independently a C_{1-6} alkoxy group that is substituted with 1 to 5 substituent(s) M; the substituents M are independently a group optionally selected from OH , a C_{1-6} alkoxy group, and a $S(O)_iR^a$ (i is an integer of 0 to 2 and R^a is a C_{1-6} alkyl group or a halogenated C_{1-6} alkyl group) group; and R^9 's are independently a group optionally selected from a halogen atom, a cyano group, a C_{1-6} alkyl group (the C_{1-6} alkyl group is optionally substituted with 1 to 5 halogen atom(s)), and a C_{1-6} alkoxy group.

[1-16-2-7] In the compound of Formula (III-1)-1 and the compound of Formula (III-1-A)-1 that are quoted in Aspect [1-16-2-5] and Aspect [1-16-2-6], J_{1a} and h are preferably in such a relationship that when J_{1a} is a nitrogen atom, h is 0 and when J_{1a} is CR^{11a} , h is an integer of 0 to 1.

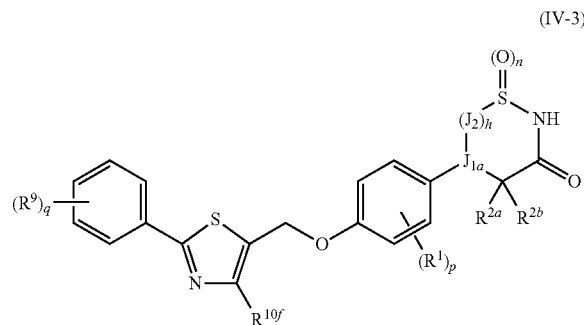
[1-16-3] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (A1)-IV and Formula (C) is Formula (c2), that is, Formula (IV-1):



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q , r , s , the ring A', R^8 , R^9 , and R^{10} are the same as defined in Formula (A) described in Aspect [1-13-c]; and $g1$ is the same as defined in Formula (A1)-IV described in Aspect [1-13-e-2]).

More specifically, preferable aspects of n , p , h , q , r , s , the ring A', J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , and $g1$ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

[1-16-3-1] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (A3)-IV and Formula (C) is Formula (c2), that is, Formula (IV-3):

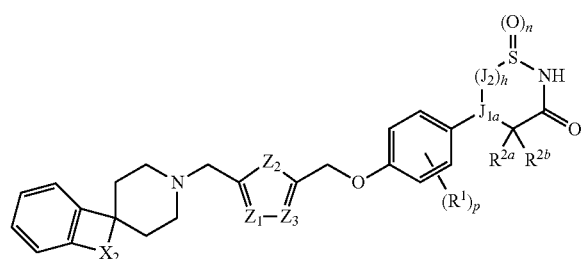


119

(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q and R^9 are the same as defined in Formula (A) described in Aspect [1-13-c]; and R^{10f} is the same as defined in Formula (A2)-IV described in Aspect [1-13-e-3]).

More specifically, preferable aspects of n , p , h , q , J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^9 , and R^{10f} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

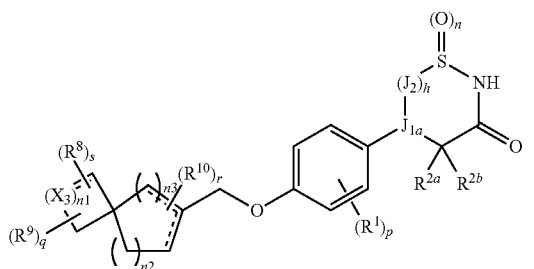
[1-16-3-2] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (A4)-IV and Formula (C) is Formula (c2), that is, Formula (IV-4):



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and Z_1 , Z_2 , Z_3 , and X_2 are the same as defined in Formula (A4)-IV described in Aspect [1-13-e-8]).

More specifically, preferable aspects of n , p , h , J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , Z_1 , Z_2 , Z_3 , and X_2 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

[1-16-4] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (A)-V and Formula (C) is Formula (c2), that is, Formula (V):



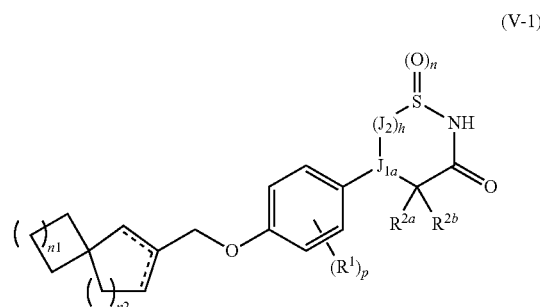
(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q and s are the same as defined in Formula (A) described in Aspect [1-13-c]; r is the same as defined in Formula (AA) described in Aspect [1-13-d]; and R^8 , R^9 , R^{10} , $n1$, $n2$, $n3$, X_3 , and the broken lines are the same as defined in Formula (A)-V described in Aspect [1-13-f]).

More specifically, preferable aspects of n , p , h , q , r , s , J_2 , R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , $n1$, $n2$, $n3$, and X_3 are the same as the

120

preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

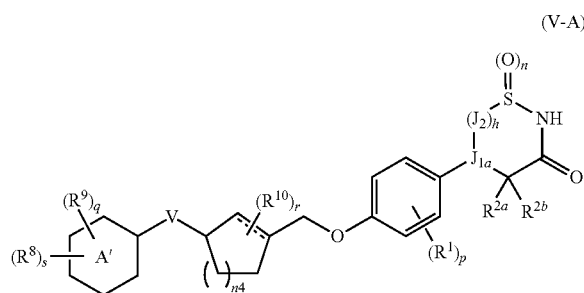
[1-16-4-1] The compound of Formula (V) according to Aspect [1-16-4] is further preferably Formula (V)-1:



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and $n1$ and $n2$ are the same as defined in Formula (A)-V described in Aspect [1-13-f]).

More specifically, preferable aspects of n , p , h , J_{1a} , J_2 , $n1$, $n2$, R^1 , R^{2a} , and R^{2b} are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

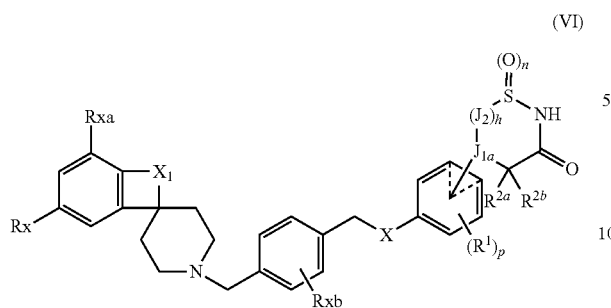
[1-16-4-2] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (AA1)-V and Formula (C) is Formula (c2), that is, Formula (V-A):



(where n , p , h , J_2 , R^1 , R^{2a} , and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q , s , the ring A', V , R^8 , and R^9 are the same as defined in Formula (A) described in Aspect [1-13-c]; r is the same as defined in Formula (AA) described in Aspect [1-13-d]; R^{10} and the broken lines are the same as defined in Formula (A)-V described in Aspect [1-13-f]; and $n4$ is the same as defined in Formula (AA)-V described in Aspect [1-13-f-8]).

More specifically, preferable aspects of n , p , h , q , r , s , the ring A', V , J_{1a} , J_2 , R^1 , R^{2a} , R^{2b} , R^8 , R^9 , R^{10} , and $n4$ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

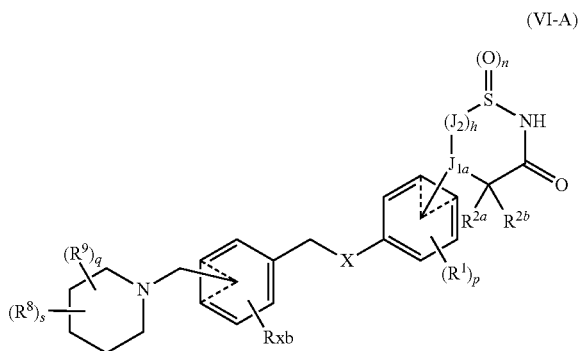
[1-16-5] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (A)-VI, that is, Formula (VI):



(where X, n, p, h, J₂, R¹, R^{2a}, R^{2b}, and the broken lines are the same as defined in Formula (I) described in Aspect [1]; J_{1a} is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; and Rx, Rxa, Rxb, and X₁ (including Ry and Rz) are the same as defined in Formula (A)-VI described in Aspect [1-13-g]). Preferable aspects of X, n, p, h, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, Rx, Rxa, Rxb, and X₁ are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

Here, as preferable aspects and specific examples of the Partial Structural Formula (A)-VI moiety having a substituted spiropiperidinylmethyl group described in Aspect [1-13-g], the same as the preferable aspects and specific examples described in Aspects [1-13-g] and [1-13-g-1] can be mentioned.

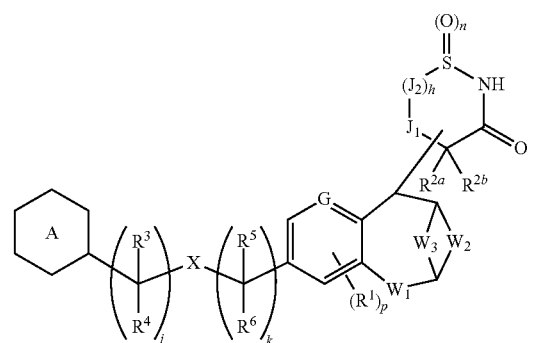
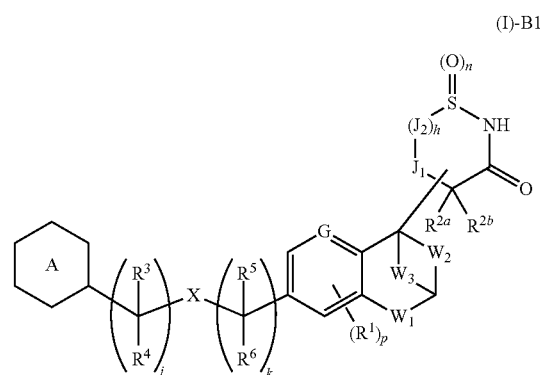
[1-16-5-1] As the compound of Formula (I) according to Aspect [1], a preferable compound is a compound in which the ring A is Formula (AA)-VI, that is, Formula (VI-A):



(where X, n, p, h, J₂, R¹, R^{2a}, and R^{2b} are the same as defined in Formula (I) described in Aspect [1]; J₁, is the same as defined in Formula (B)-1 described in Aspect [1-14-a-1]; q, s, R⁸, and R⁹ are the same as defined in Formula (A) described in Aspect [1-13-c]; R_xb is the same as defined in Formula (A)-VI described in Aspect [1-13-g]; and the broken lines are the binding position of an isothiazolyl group or a piperidinyl-methyl group).

More specifically, preferable aspects of X, n, p, h, q, s, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R⁸, R⁹, and Rxb are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof.

[1-17] As the compound of Formula (I) according to Aspect [1], a preferable compound is Formula (I)-B1 or Formula (I)-B2:



(where n, p, h, j, k , the ring $A, X, J_1, J_2, R^1, R^{2a}, R^{2b}, R^3, R^4, R^5$, and R^6 are the same as defined in Formula (I) described in Aspect [1]; and G, W_1, W_2 , and W_3 are the same as in Formula (BB1) or Formula (BB2) described in Aspect [1-10]).

More specifically, preferable aspects of n , p , h , j , k , the ring A , X , J_1 , J_2 , R^1 , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , and R^6 are the same as the preferable aspects described in any one of Aspects [1-1] to [1-15] and subordinate Aspects thereof. Preferable aspects of G , W_1 , W_2 , and W_3 are the same as the preferable aspects described in Aspect [1-10] and subordinate Aspects thereof.

[1-17-a] As the compound of Formula (I)-B1 or Formula (I)-B2, a preferable compound is a compound in which the ring A is a C₆₋₁₄ aryl group which is optionally substituted with 1 to 5 L(s) or a 3- to 14-membered heterocyclic group which is optionally substituted with 1 to 5 L(s) and the linker moiety containing X is Formula (c1) or Formula (c4) described in Aspect [1-15].

A more preferable compound thereof is a compound in which the ring A is a phenyl group which is optionally substituted with 1 to 5 L(s), a phthalaziny group which is optionally substituted with 1 to 5 L(s), or Formula (A)-VIII described in Aspect [1-13-j] and the linker moiety containing X is Formula (c1).

A further preferable compound thereof is a compound in which the ring A is a phenyl group (the phenyl group is optionally substituted with 1 to 3 halogen atom(s), 1 to 3 cyano group(s), 1 to 3 C₁₋₆ alkyl group(s), 1 to 3 halogenated C₁₋₆ alkyl group(s), 1 to 3 C₁₋₆ alkoxy group(s), or 1 to 3 —SF₅), a phthalaziny group (the phthalaziny group is optionally substituted with 1 to 3 halogen atom(s), 1 to 3 cyano group(s), 1 to 3 C₁₋₆ alkyl group(s), 1 to 3 halogenated C₁₋₆ alkyl group(s), 1 to 3 C₁₋₆ alkoxy group(s), or 1 to 3-SF₅), or Formula (A)-VIII and the linker moiety containing X is Formula (c1).

[1-18] As described above, Aspects [1-1] to [1-17] and subordinate Aspects thereof of the present invention, respec-

123

tive preferable aspects described above, and the definitions of the substituents can be optionally combined, so that the preferable aspects of the compound of Formula (I) according to Aspect [1] can be optionally provided.

[1-19] Examples of preferable compounds as the compound of Formula (I) according to Aspect [1] include the following:

5-[4-[[3-[4-(2-ethoxyethoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 1);

5-[4-[[3-[4-(2-ethoxyethoxy)-3-fluoro-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 2);

5-[4-[[3-[3-fluoro-4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 3);

5-[4-[[3-[4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 4);

5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 5);

5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one trifluoro acetic acid salt (Example 6);

5-[4-[[3-[4-(3-hydroxy-3-methylbutoxy)-2,5-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 7);

5-[4-[[3-[4-(3-hydroxypropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 8);

5-[4-[[3-[4-[(2R)-2,3-dihydroxypropoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 9);

5-[4-[[3-[4-[3-hydroxy-2-(hydroxymethyl)propoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 10);

5-[4-[[3-[4-(3-aminopropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one trifluoro acetic acid salt (Example 11);

5-[4-[[3-[4-[(3R)-3-hydroxybutoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 12);

5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (Example 13);

5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Example 14);

5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Example 15);

5-[2-chloro-4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Example 16);

5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]-2-methylphenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Example 17);

5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-4-methyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Example 18);

5-[4-[[3-(2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one (Example 19);

5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one (Example 20);

124

5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one (Example 21);

5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one (Example 22);

A compound selected from:

5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A) (Example 23);

5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)-a (Example 23 (A)-a);

5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)-b (Example 23 (A)-b);

5-[4-[[3-[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A) (Example 24);

5-[4-[[3-[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a (Example 24 (A)-a);

5-[4-[[3-[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-b (Example 24 (A)-b);

4-(((1R)-1-(4-(1-oxo-1,2-thiazolidin-3-one-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A) (Example 25);

4-(((1R)-1-(4-(1-oxo-1,2-thiazolidin-3-one-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A)-a (Example 25 (A)-a);

4-(((1R)-1-(4-(1-oxo-1,2-thiazolidin-3-one-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A)-b (Example 25 (A)-b);

4-(((1R)-1-(4-(1,1-dioxo-1,2,6-thiadiazinan-3-one-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (Example 26);

5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (Example 27);

5-(4-(((R)-4-(trifluoromethyl)-2,3-dihydrobenzofuran-3-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (Example 28);

5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (Example 29);

5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (Example 30);

5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one (Example 31);

4-(((1R)-1-(4-(1,1-dioxo-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (Example 32);

5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one (Example 33);

5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one (Example 34);

5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one (Example 35);

5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 36);

5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 37);

5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 38);

125

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 39);

5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 40);

5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (D) (Example 41);

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 42);

5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 43);

5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 44);

5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 45);

5-(4-(((R)-4-(4-methoxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 46);

5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 47);

5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (Example 48);

5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C) (Example 49);

4-(((1R)-1-(4-(1,1-dioxide-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (C) (Example 50);

3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A) (Example 51);

3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1,4-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 51 (A)-a);

3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-b (Example 51 (A)-b);

3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A) (Example 52);

3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 52 (A)-a);

3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-b (Example 52 (A)-b);

3-hydroxy-5-(4-(((R)-4-(m-tolyl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A) (Example 53);

3-hydroxy-5-(4-(((R)-4-(m-tolyl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 53 (A)-a);

3-hydroxy-5-(4-(((R)-4-(m-tolyl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-b (Example 53 (A)-b);

5-(4-(((R)-4-(6-(2-ethoxyethoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A) (Example 54);

126

5-(4-(((R)-4-(6-(2-ethoxyethoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 54 (A)-a);

5-(4-(((R)-4-(6-(2-ethoxyethoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-b (Example 54 (A)-b);

3-hydroxy-5-(4-(((R)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A) (Example 55);

3-hydroxy-5-(4-(((R)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 55 (A)-a);

3-hydroxy-5-(4-(((R)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-b (Example 55 (A)-b);

5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-isothiazolidine-3-one 1-oxide (A)-a (Example 56 (A)-a);

5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-isothiazolidine-3-one 1-oxide (A)-b (Example 56 (A)-b);

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 57);

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-b (Example 58);

5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 59);

5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 60);

3-hydroxy-5-(4-(((R)-4-(4-methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 61);

3-hydroxy-5-(4-(((R)-4-(2-methyl-6-(3-(methylsulfonyl)propoxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 62);

3-hydroxy-5-(4-(((R)-4-(6-methoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 63);

3-hydroxy-5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 64);

3-hydroxy-5-(4-(((R)-4-(2-trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 65);

3-hydroxy-5-(4-(((R)-4-(o-tolyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a (Example 66);

5-(4-(((R)-4-(5-fluoro-2-methylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 67);

5-(4-(((1R)-4-(2-fluoro-6-methoxyphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 68); and

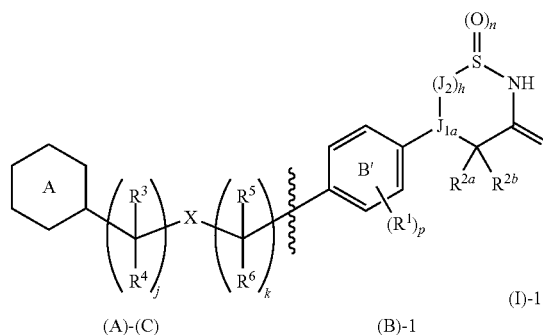
5-(4-(((R)-4-(2-ethoxy-5-fluorophenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a (Example 69),

a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable solvate of the compound or a pharmaceutically acceptable solvate of the salt, an optical isomer of the compound, a pharmaceutically acceptable salt of the isomer, and a pharmaceutically acceptable solvate of the iso-

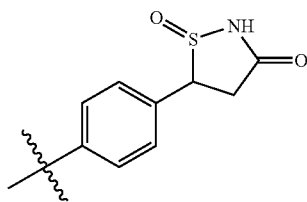
127

mer or a pharmaceutically acceptable solvate of the salt. Examples of the above preferable compounds also include the compounds of Structural Formulae 8 to 17 below in (Example 1P) to (Example 157P), a pharmaceutically acceptable salt of the compound, a pharmaceutically acceptable solvate of the compound or a pharmaceutically acceptable solvate of the salt, an optical isomer of the compound, a pharmaceutically acceptable salt of the isomer, and a pharmaceutically acceptable solvate of the isomer or a pharmaceutically acceptable solvate of the salt.

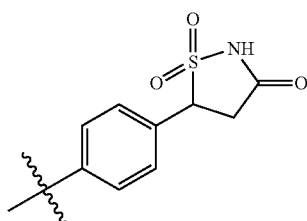
[1-19-1] In the compound of Formula (I) according to Aspect [1] or of Formula (I)-1 according to Aspect [1-16],



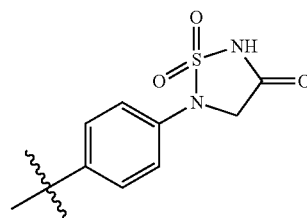
compounds produced by optionally combining the groups of Partial Structural Formula (A)-(C) (on the left of the wavy line) and Partial Structural Formula (B)-1 (on the right of the wavy line) in Formula (I)-1 below can be produced optionally. More specifically, Partial Structural Formula (B)-1 is a group optionally selected from Formula (B1a-het1) to Formula (B1a-het5) or Formula (B2a-het1) to Formula (B2a-het5) described below, and Partial Structural Formula (A)-(C) is a group optionally selected from Formula (a-1) to Formula (a-109) described below.



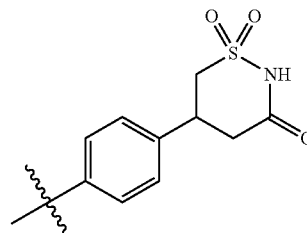
(B1a-het1)



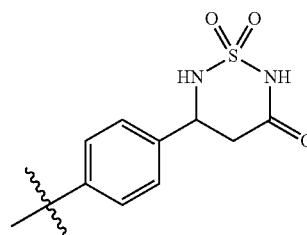
(B1a-het2)



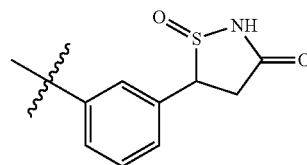
(B1a-het3)



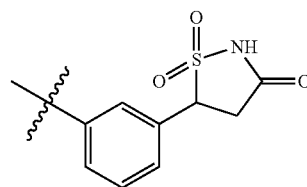
(B1a-het4)



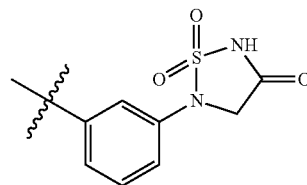
(B1a-het5)



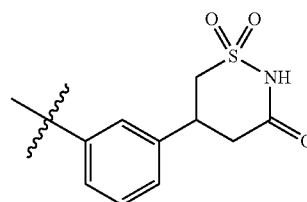
(B2a-het1)



(B2a-het2)



(B2a-het3)



(B2a-het4)

128

-continued

5

10

15

20

25

30

35

40

45

50

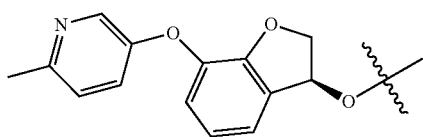
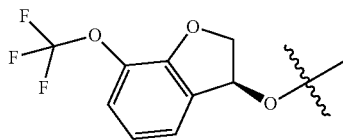
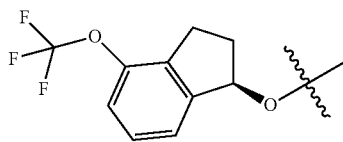
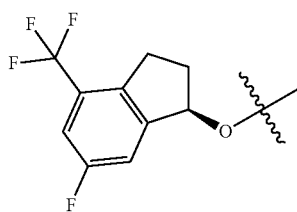
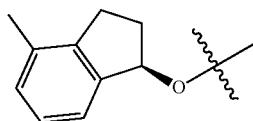
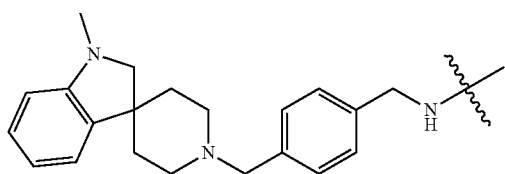
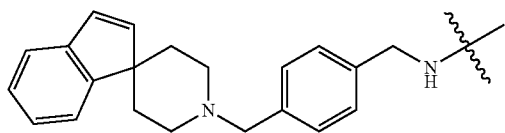
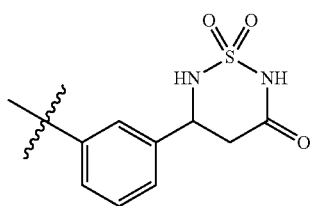
55

60

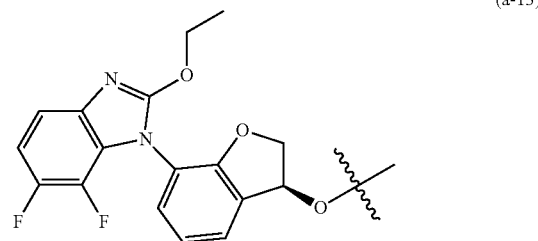
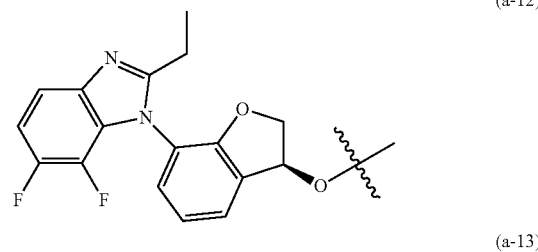
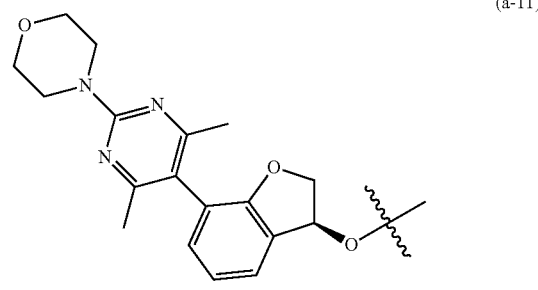
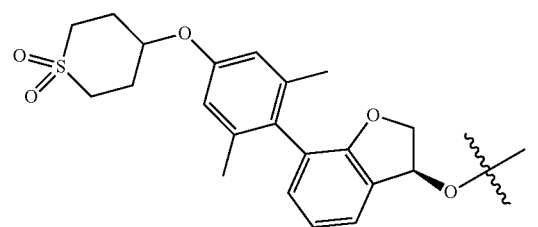
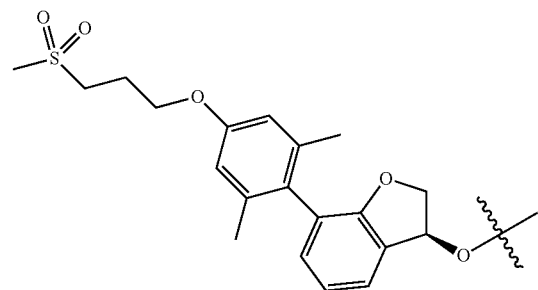
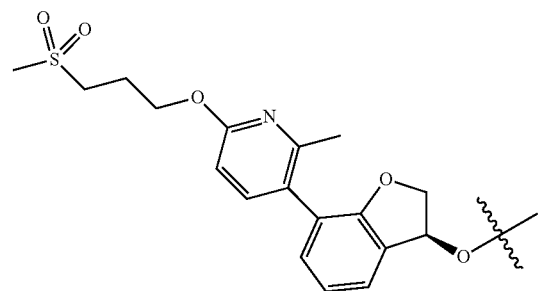
65

129

-continued

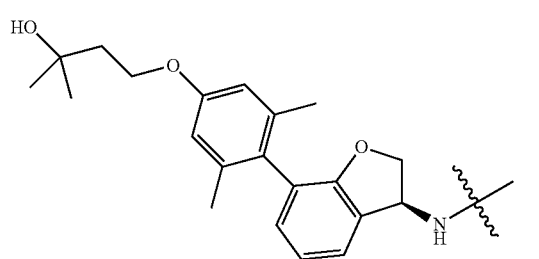
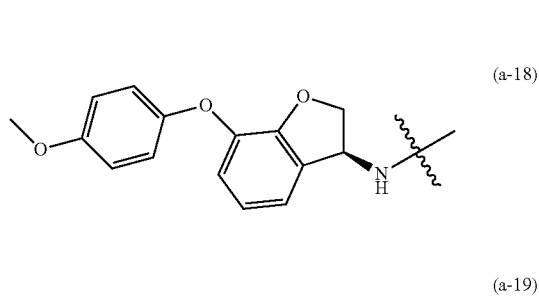
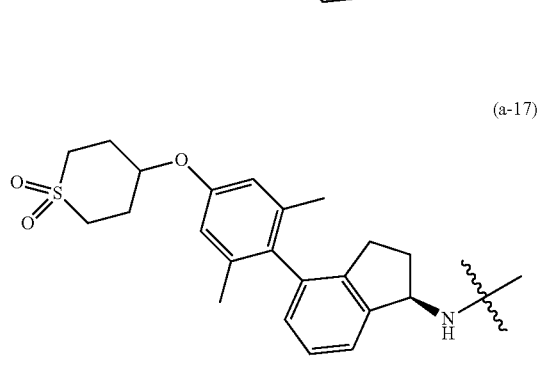
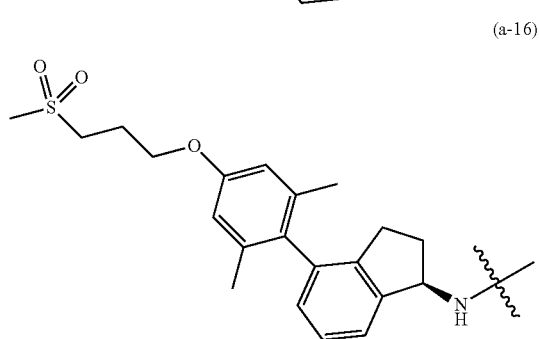
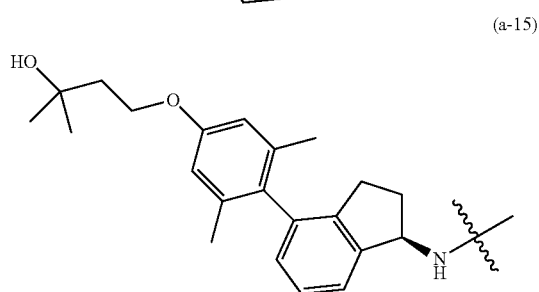
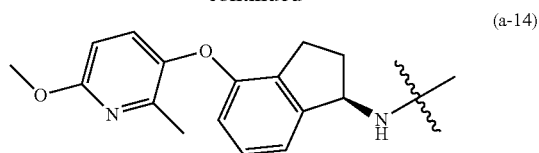
**130**

-continued

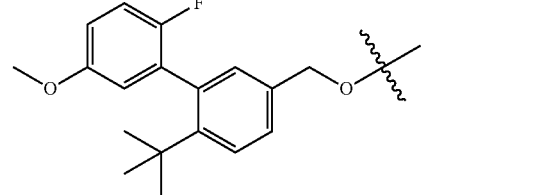
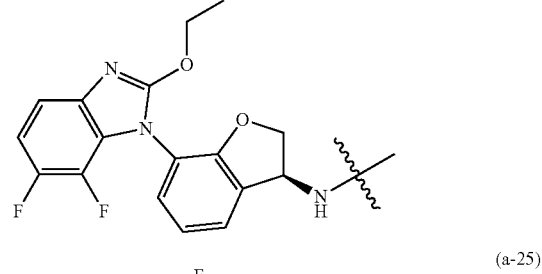
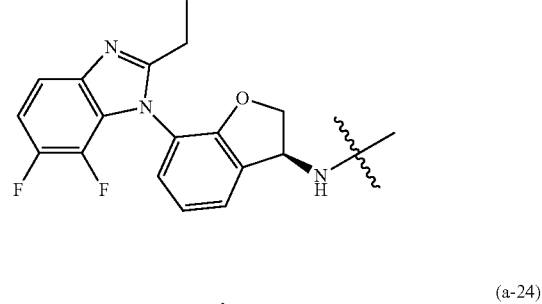
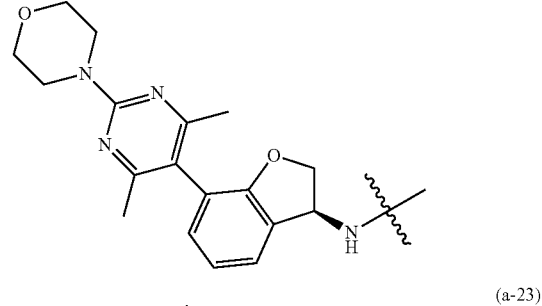
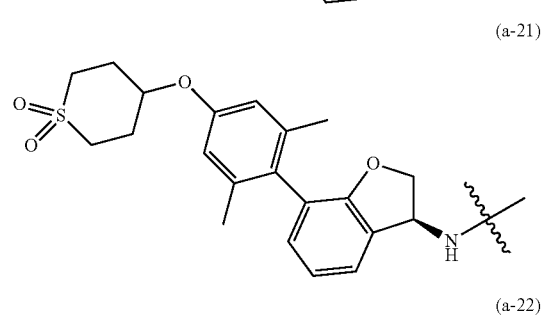
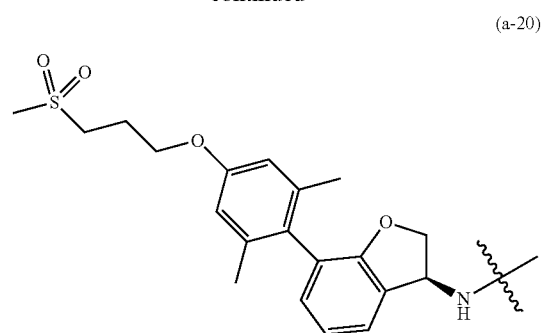


131

-continued

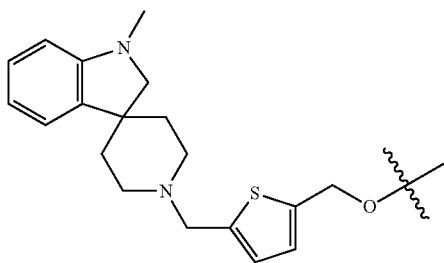
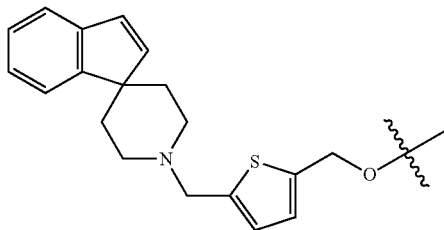
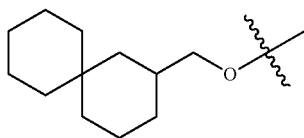
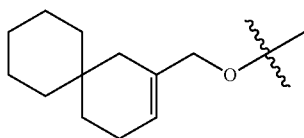
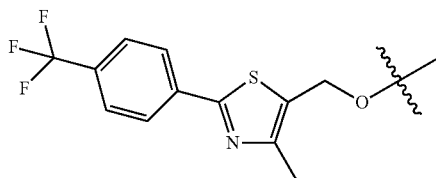
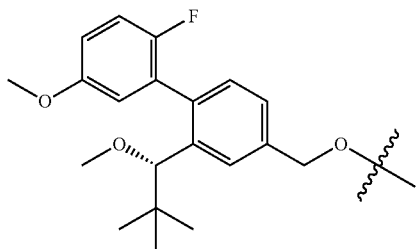
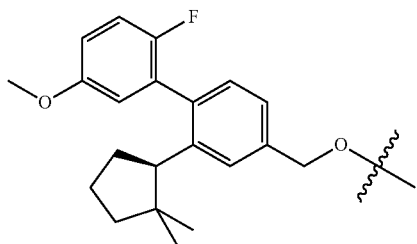
**132**

-continued



133

-continued

**134**

-continued

(a-26)

5

10

(a-27)

15

20

(a-28)

25

(a-29)

35

(a-30)

40

(a-31)

50

55

(a-32)

60

65

(a-33)

(a-34)

(a-35)

(a-36)

(a-37)

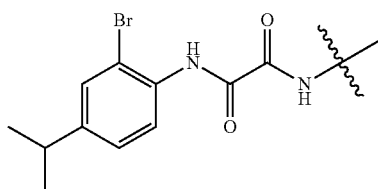
(a-38)

(a-39)

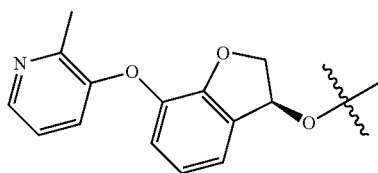
(a-40)

135

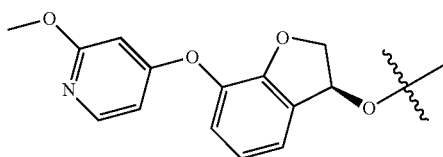
-continued



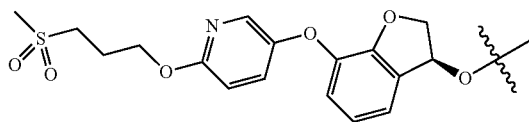
5



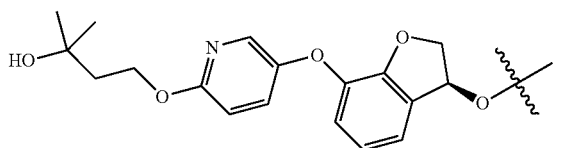
10



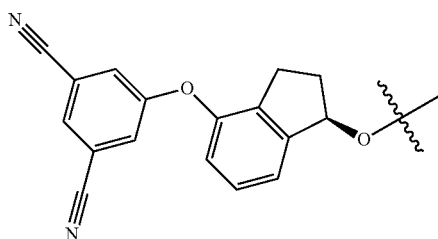
20



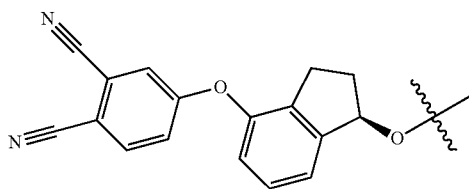
25



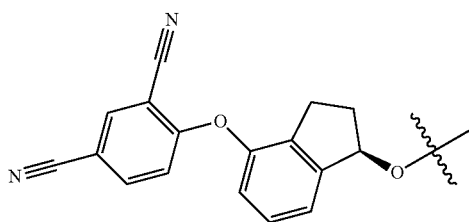
35



40



50



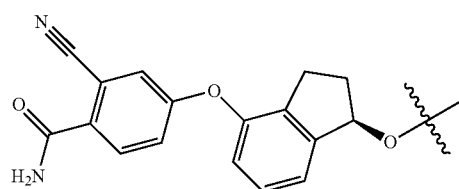
55

60

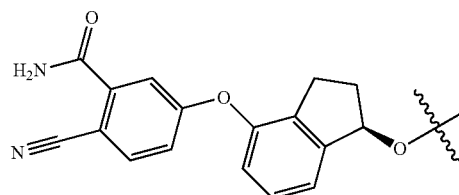
65

136

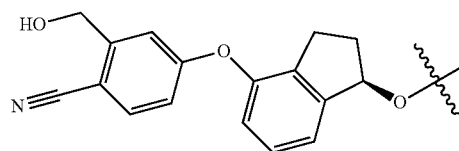
-continued



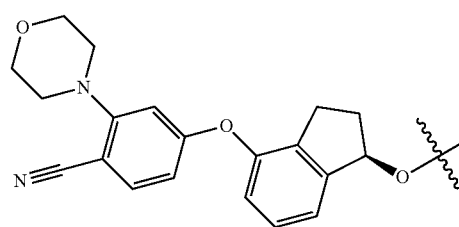
(a-49)



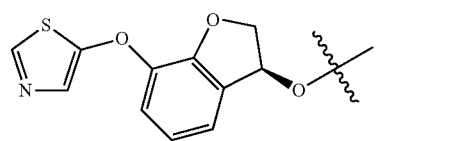
(a-50)



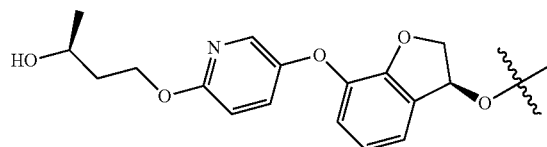
(a-51)



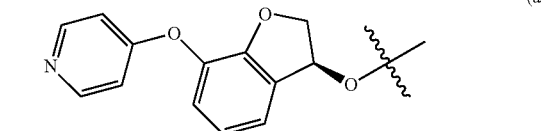
(a-52)



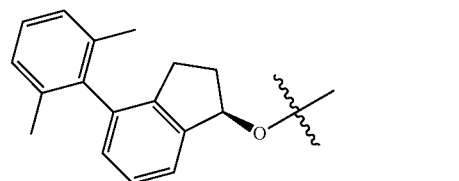
(a-53)



(a-54)



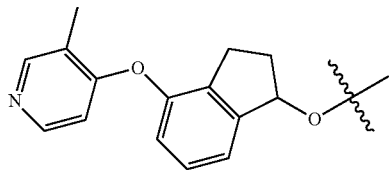
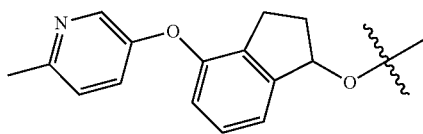
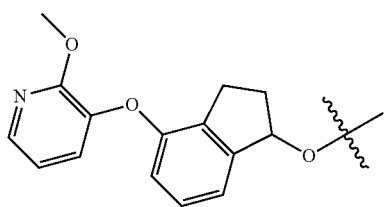
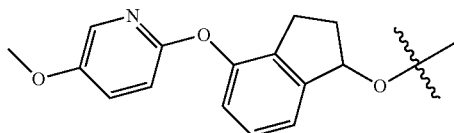
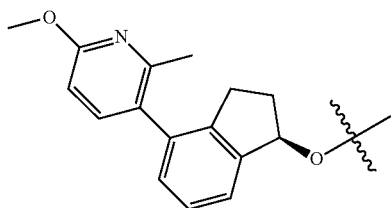
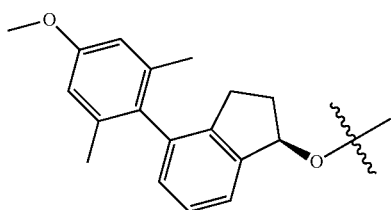
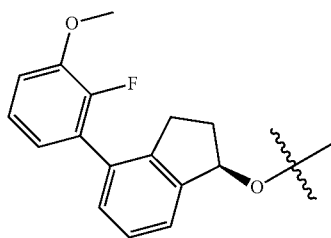
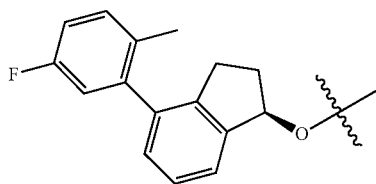
(a-55)



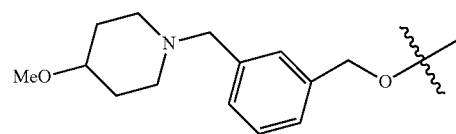
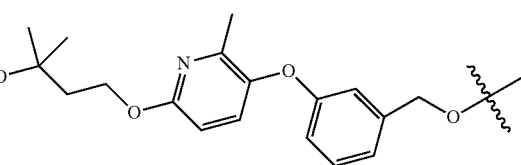
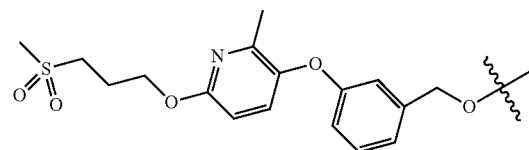
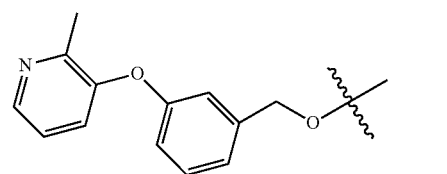
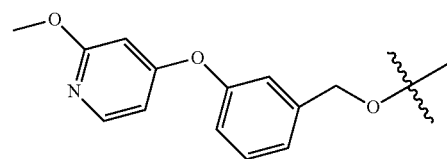
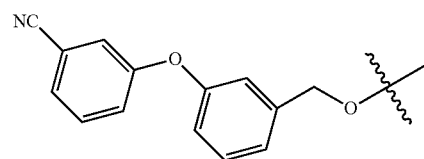
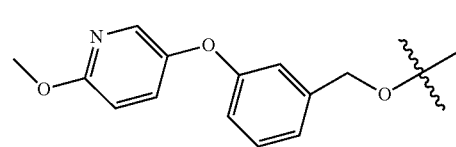
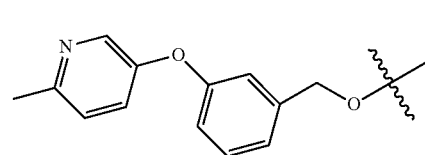
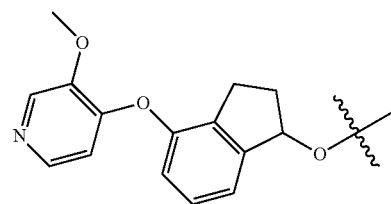
(a-56)

137

-continued

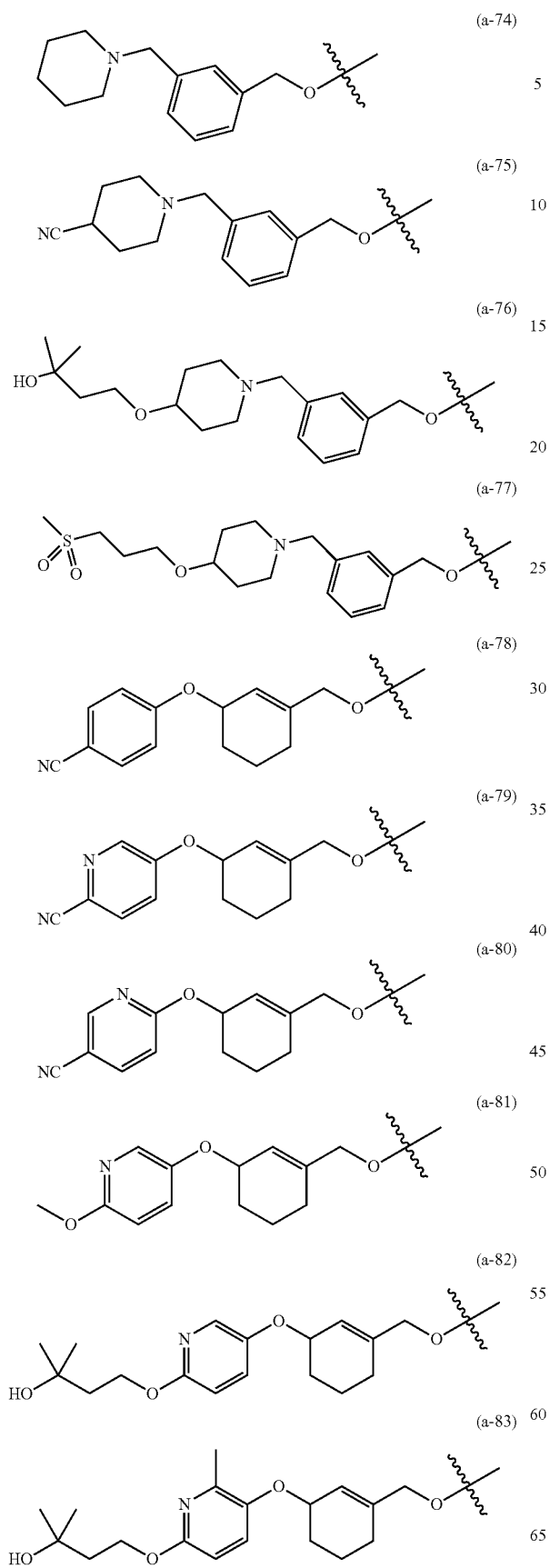
**138**

-continued

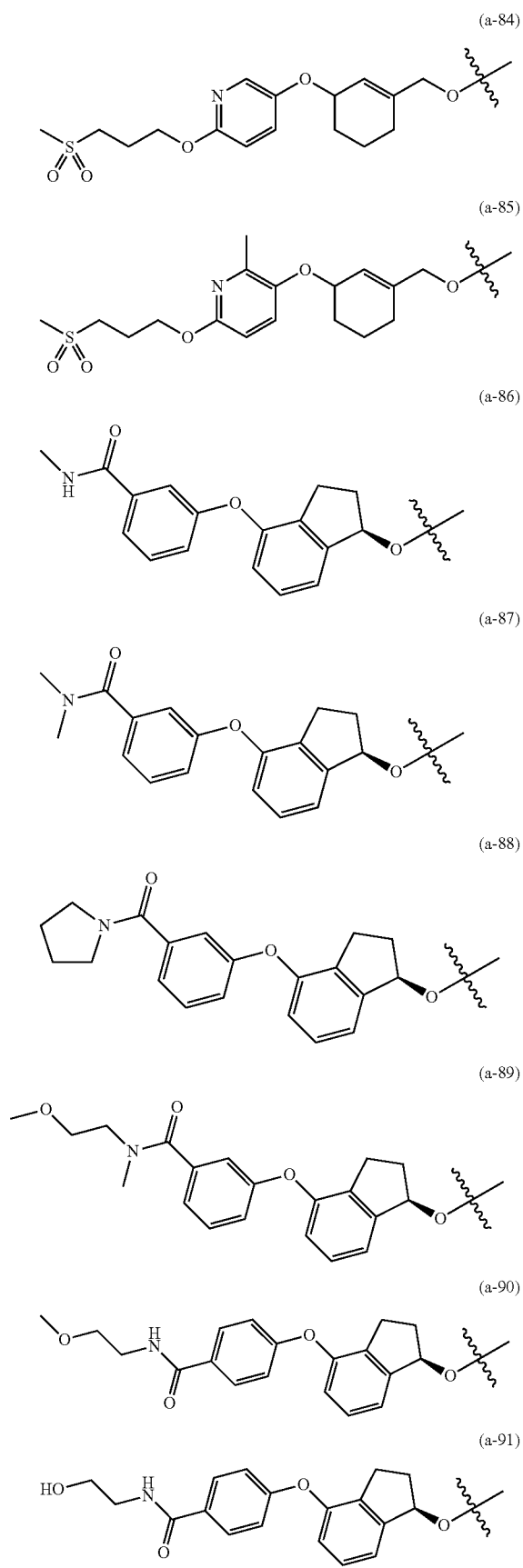


139

-continued

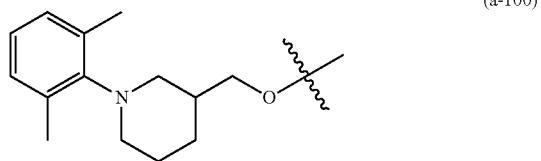
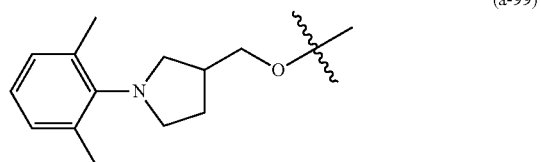
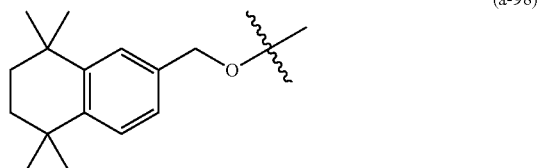
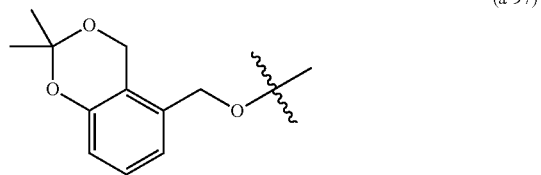
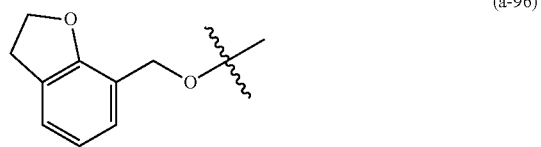
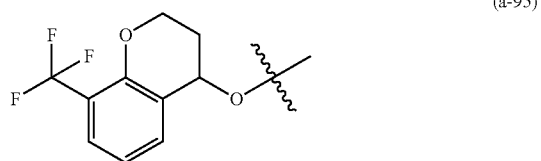
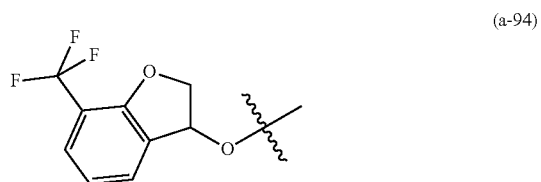
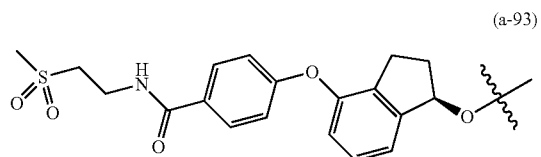
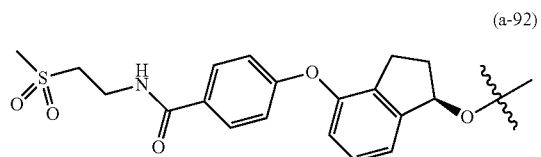
**140**

-continued

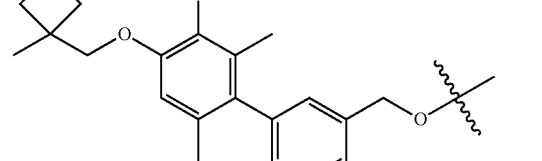
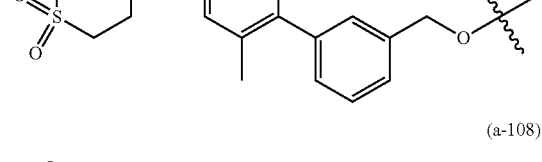
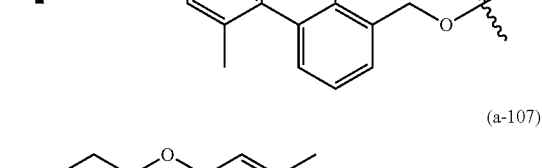
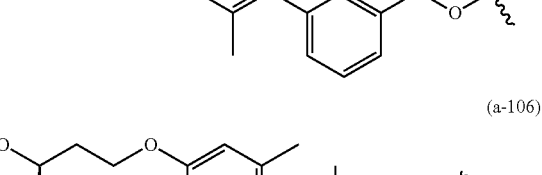
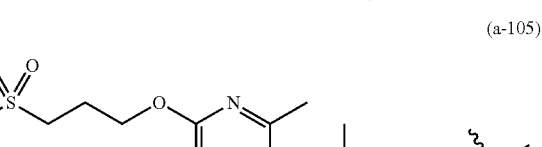
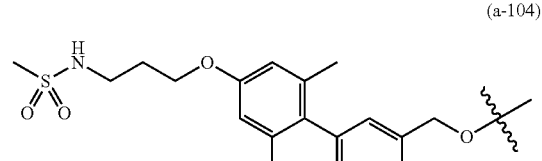
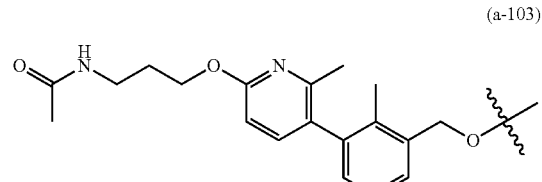
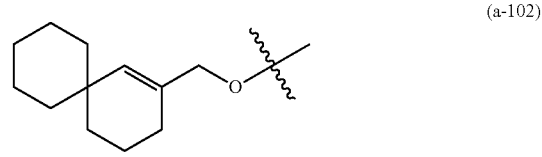
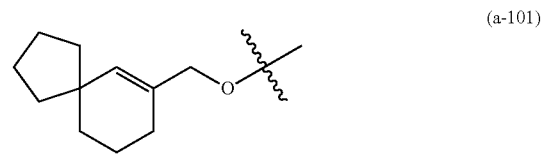


141

-continued

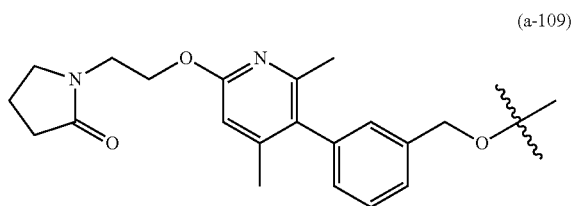
**142**

-continued

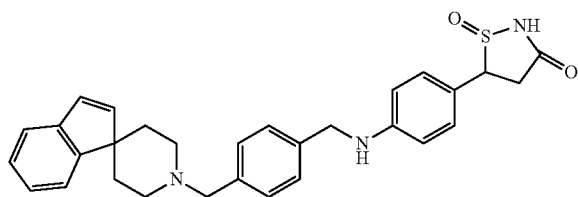


143

-continued

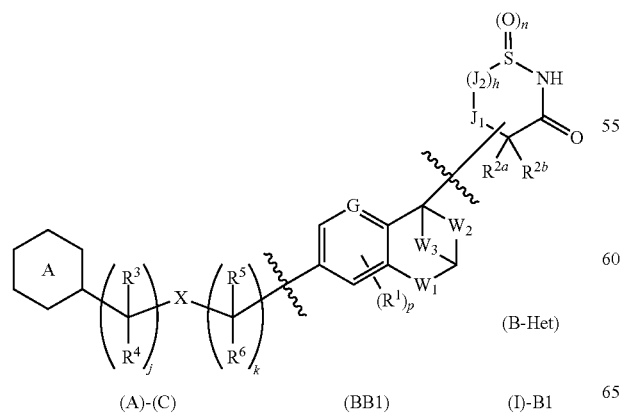


The compounds produced by combining these partial structural formulae are exemplified as specific compounds of the compound of Formula (I) or Formula (I)-1. For example, a compound of Formula (a1-B1a-het1):

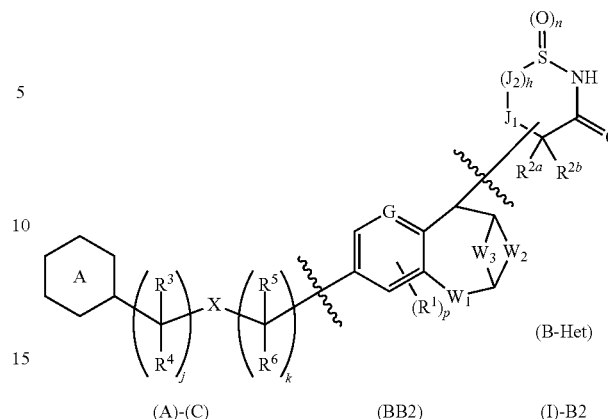


produced by combining Formula (B1a-het1) with Formula (a-1) is exemplified as the specific compound. In such a specific compound, a compound in which the moiety corresponding to X is exchanged from an oxygen atom to —NH— or from —NH— to an oxygen atom can also be optionally produced, and the thus produced compound is also exemplified as the specific compound.

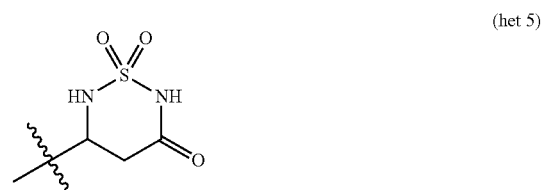
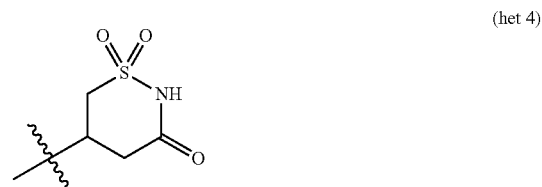
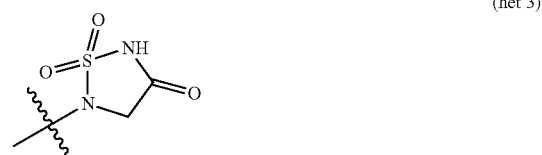
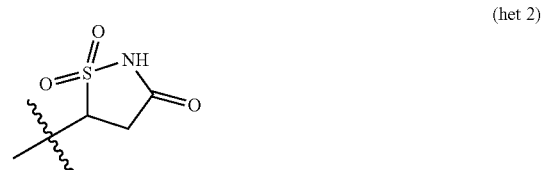
[1-19-2] In the compound of Formula (I) according to Aspect [1] or of Formula (I)-B 1 or Formula (I)-B2 according to Aspect [1-17], compounds produced by optionally combining the groups of Partial Structural Formula (A)-(C) (on the left of the left wavy line), Partial Structural Formula (BB1) or Formula (BB2) (between the two wavy lines), Partial Structural Formula (B-Het) (on the right of the right wavy line) in Formula (I)-B 1 or Formula (I)-B2 can also be produced optionally:

**144**

-continued

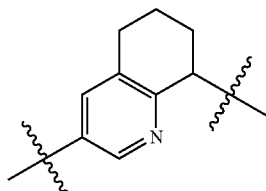
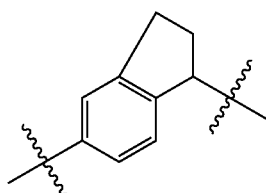
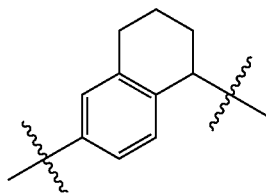
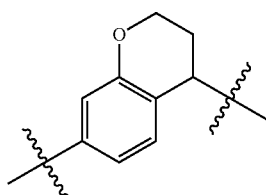
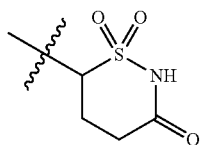
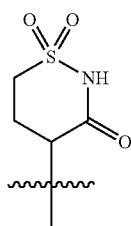
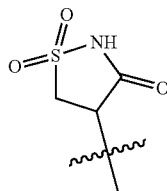
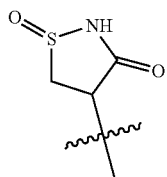


More specifically, Partial Structural Formula (B-Het) is a group optionally selected from Formula (het1) to Formula (het9). Partial Structural Formula (BB1) or Formula (BB2) is a group optionally selected from Formula (b-1) to Formula (b-5), and Partial Structural Formula (A)-(C) is a group optionally selected from Formula (a-37) to Formula (a-40) exemplified in Aspect [1-19-1] or Formula (a-94) to Formula (a-99) below.



145

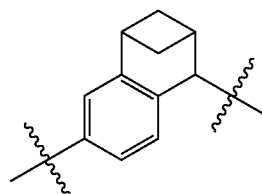
-continued

**146**

-continued

(het 6)

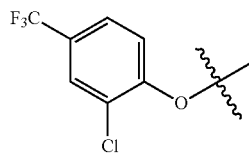
5



(b-5)

(het 7)

10

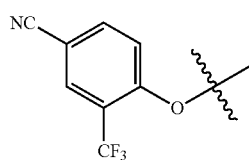


(a-94)

15

(het 8)

20

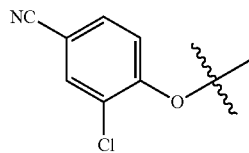


(a-95)

25

(het 9)

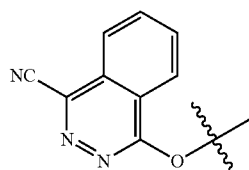
30



(a-96)

(b-1)

35

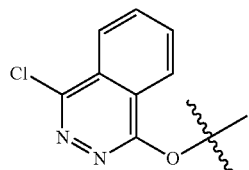


(a-97)

40

(b-2)

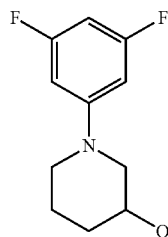
45



(a-98)

(b-3)

50

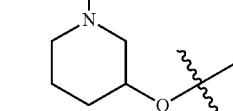


(a-99)

55

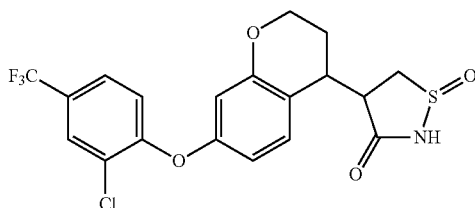
(b-4)

60



The compounds produced by combining these partial structural formulae are exemplified as specific compounds of the compound of Formula (I), Formula (I)-B1, or Formula (I)-B2. For example, a compound of Formula (a94-b1-het6):

147



produced by combining Formula (het6), Formula (b-1), and Formula (a-94) is exemplified as the specific compound.

[2] A second aspect of the present invention is a pharmaceutical composition containing the compound of Formula (I), a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable solvate of the compound or a pharmaceutically acceptable solvate of the salt.

[3] A third aspect of the present invention is a prophylactic agent and/or a therapeutic agent for a GPR40-involving disease, characterized by containing, as an active ingredient, at least one of the compound of Formula (I), a pharmaceutically acceptable salt of the compound, and a pharmaceutically acceptable solvate of the compound and a pharmaceutically acceptable solvate of the salt.

[3-1] Specifically, the third aspect of the present invention is a prophylactic agent and/or a therapeutic agent for each disease of diabetes [more specifically, any one of or all of Type 1 diabetes (insulin-dependent diabetes), Type 2 diabetes (non-insulin-dependent diabetes), and borderline type diabetes (impaired glucose tolerance (IGT) and/or impaired fasting glycemia (IFG))], obesity, and adiposity, characterized by containing, as an active ingredient, at least one of the compound of Formula (I), a pharmaceutically acceptable salt of the compound, and a pharmaceutically acceptable solvate of the compound and a pharmaceutically acceptable solvate of the salt. An inhibitor of Type 2 diabetes in the impaired glucose tolerance is also included in examples of the above prophylactic agent and therapeutic agent. A therapeutic agent for sulfonylurea secondary failure diabetes is also included in the examples thereof, and by the therapeutic agent, also in (administration-ineffective) diabetic patients who cannot obtain a satisfactory hypoglycemic effect even by being administered with a sulfonylurea agent (such as glibenclamide and glimepiride) or a rapid-acting insulin secretagogues (such as mitiglinide), insulin secretion effect or hypoglycemic effect can be obtained.

Here, in relationship between the blood glucose level and the disease, the diabetes is characterized by exhibiting a fasting blood glucose level of 126 mg/dL or more, or a casual blood glucose level or a 2 hours value of the 75 g oral glucose tolerance test (OGTT) of 200 mg/dL or more. The borderline type diabetes (also called glucose tolerance disorders) refers to an impaired fasting glycemia (IFG) in which the fasting blood glucose level is 110 mg/dL or more and less than 126 mg/dL and/or an impaired glucose tolerance (IGT) in which a 2 hours value of the 75 g OGTT is 140 mg/dL or more and less than 200 mg/dL.

The insulin resistance refers to a pathological condition in which insulin becomes unable to lower the blood glucose level in the organism and is evaluated by a quantitative glucose clamp technique or HOMA-IR in clinical practice. It is known that the insulin resistance causes a hyperinsulinemia and becomes a risk of a hypertension and a coronary artery disease.

The "adiposity" is defined by the Japan Society for the Study of Obesity as "a pathological condition requiring medi-

148

cally a weight reduction in the case where an obesity-derived or -related health impairment is combined or such a combination is expected". The "obesity" defined here is evaluated by measuring BMI (body mass index, kg/m²). Generally, a body having a BMI of 25 or more is diagnosed as obesity. Examples of the result of the therapy include the reduction of BMI.

[4] A fourth aspect of the present invention is an insulin secretagogue, characterized by containing, as an active ingredient, at least one of the compound of Formula (I), a pharmaceutically acceptable salt of the compound, and a pharmaceutically acceptable solvate of the compound and a pharmaceutically acceptable solvate of the salt.

[5] A fifth aspect of the present invention is a GPR40 activating agent containing one or more of the compound of Formula (I), a pharmaceutically acceptable salt of the compound, and a pharmaceutically acceptable solvate of the compound and a pharmaceutically acceptable solvate of the salt.

In the second to fifth aspects and preferable aspects thereof, more preferable substituents and a combination thereof in Formula (I) are according to descriptions described in the first aspect.

In each aspect as described in [1] to [5] of the present invention, it is preferable to use a compound having a EC₅₀ value of preferably, 3 μM or less, more preferably, 1 μM or less, further preferably, 300 nM or less, and most preferably, 100 nM or less, when the GPR40 agonist action is measured by a method accordingly selected (for example, the below described pharmacological test example 1 (an agonist action on GPR40 of human origin)).

In the above aspects of the present invention, the "therapeutic agent" is not only for treating diseases or symptoms, but also for improving diseases or symptoms.

In all of the above aspects, when the term "compound" is used, the compound refers also to a "pharmaceutically acceptable salt of the compound". In addition, there is the case where the compound of the present invention has an asymmetric carbon, and thus, the compound of the present invention includes a mixture of various stereoisomers such as a geometric isomer, a tautomer, and an optical isomer, and an isolated stereoisomer.

The compound of Formula (I) may have an axial asymmetry due to a steric hindrance and an isomer caused by the axial asymmetry (axial chirality) is also included in the compound of the Formula (I). The isolation and the purification of such stereoisomers can be performed by a person skilled in the art by an ordinary technique through an optical resolution or an asymmetric synthesis using a preferential crystallization or a column chromatography.

The compound of Formula (I) of the present invention may form an acid addition salt or a salt with a base depending on the type of the substituent. Such salt is not particularly limited so long as the salt is a pharmaceutically acceptable salt. Specific examples thereof include acid addition salts with: mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic carboxylic acids, for example, an aliphatic monocarboxylic acid such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, enanthic acid, capric acid, myristic acid, palmitic acid, stearic acid, lactic acid, sorbic acid, and mandelic acid, an aromatic monocarboxylic acid such as benzoic acid and salicylic acid, an aliphatic dicarboxylic acid such as oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, malic acid, and tartaric acid, an aliphatic tricarboxylic acid such as citric acid, cinnamic acid, glycolic acid, pyruvic acid, oxalic acid, salicylic acid, and N-acetylcysteine; organic sulfonic acids, for example, an aliphatic sul-

fonic acid such as methanesulfonic acid, ethanesulfonic acid, and 2-hydroxyethanesulfonic acid, and an aromatic sulfonic acid such as benzenesulfonic acid and p-toluenesulfonic acid; and acidic amino acids such as aspartic acid and glutamic acid, salts (including, besides mono salts, disodium salts and dipotassium salts) with a metal, for example, alkali metals such as lithium, sodium, potassium, and cesium, and alkaline earth metals such as magnesium, calcium, and barium, salts with a metal such as aluminum, iron, copper, nickel, cobalt, and zinc, salts with an organic base such as methylamine, ethylamine, tert-butylamine, tert-octylamine, diethylamine, triethylamine, cyclohexylamine, dibenzylamine, ethanolamine, diethanolamine, triethanolamine, piperidine, morpholine, pyridine, lysine, arginine, ornithine, ethylenediamine, N-methylglucamine, glucosamine, a phenylglycine alkyl ester, and guanidine, and salts with glycine, histidine, choline, and ammonium.

These salts can be obtained by an ordinary method including, for example, mixing an equivalent of the compound of the present invention with a solution containing a desired acid, base, or the like, and collecting a desired salt by filtration or distillation-off of a solvent. The compound of the present invention or a salt of the compound can form a solvate with a solvent such as water, ethanol, and glycerol.

The salt of the compound of the present invention includes a mono-salt and a di-salt. The compound of the present invention can form both of an acid addition salt and a salt with a base simultaneously depending on the type of the substituent in the side chains. Further, the present invention encompasses also hydrates, various pharmaceutically acceptable solvates, and crystal polymorphs of the compound of Formula (I) of the present invention. Here, needless to say, the present invention is not limited to the compounds described in Examples below and encompasses all of the compounds of Formula (I) of the present invention and pharmaceutically acceptable salts of the compounds.

The compound of the present invention may be labeled with an isotope (such as ^3H , ^{14}C , and ^{35}S).

[Method for Producing the Compound of the Present Invention]

Methods for producing the compound of Formula (I) of the present invention will be described below.

The compound of Formula (I) of the present invention, a salt of the compound, and a solvate of the compound or the salt can be produced by a combination of commonly known chemical production methods. Typical production methods will be described below.

In each Formula in the production methods below, each definition of ring A, ring B, ring A', ring A'', ring A''', ring B', X, V, J₁, J_{1a}, J₂, R¹, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R^{12c}, R¹³, R^{13a}, R¹⁴, n, p, q, q1, q2, r, r1, s, h, j, k, f, g, g1, X₃, n1, n2, n3, n4, Z₁, Z₂, Z₃, Rx, Rxa, Rxb, X₁, and the like is the same as each definition in Formula (I), Formula (A), Formula (A)-I, Formula (AA), Formula (A1)-IV, Formula (A2)-IV, Formula (A)-V, Formula (AA)-V, Formula (A)-VI, and Formula (B)-I described in the first aspect above unless otherwise specified.

In the production methods, the definition of m is an integer of 1 or 2.

In the production methods, the definition of h2 is an integer of 0 to 2.

In the production methods, the definition of g-1 is an integer of 0 to 3.

In the production methods, the definition of R' is a C₁₋₆ alkyl group such as a methyl group, an ethyl group, and a t-butyl group unless otherwise specified.

In the production methods, the definition of R'' is a hydrogen atom, a hydroxy group, or a C₁₋₆ alkoxy group such as a methoxy group and an ethoxy group unless otherwise specified.

In the production methods, each definition of Y, Y₁, and Y₂ is a halogen atom, a nitro group, a protected imino group ($-\text{NP}^1_2$), a formyl group, or an ester group unless otherwise specified.

In the production methods, the definition of Z is a leaving group including a hydroxy group, a halogen atom, and a sulfonyloxy group such as a methanesulfonyloxy group, a p-toluenesulfonyloxy group, and a trifluoromethanesulfonyloxy group unless otherwise specified.

In the production methods, the definition of W is boronic acid, a boronic ester, or a trifluoroborate salt unless otherwise specified.

In the production methods, for the definitions of W¹ and W², W² is boronic acid, a boronic ester, or a trifluoroborate salt when W¹ is a hydroxy group, a halogen atom, or a trifluoromethanesulfonyloxy group, and W² is a hydroxy group, a halogen atom, or a trifluoromethanesulfonyloxy group when W¹ is boronic acid, a boronic ester, or a trifluoroborate salt unless otherwise specified.

In the production methods, the definition of * is a chiral center.

In the production methods, each definition of P¹, P², P³, P⁴, and P⁵ is a protective group for a hydroxy group ($-\text{OH}$), a thiol group ($-\text{SH}$), or an imino group ($-\text{NH}-$) unless otherwise specified. Examples of the protective group for a hydroxy group include an alkyl group such as a methyl group; an alkoxyalkyl group such as a methoxymethyl group, a methoxyethoxymethyl group, and a tetrahydropyranyl group; an arylmethyl group such as a benzyl group and a triphenylmethyl group; a silyl group such as a trimethylsilyl group, a triethylsilyl group, and a t-butyltrimethylsilyl group; an alkanoyl group such as an acetyl group and a pivaloyl group; an aroyl group such as a benzoyl group; an alkoxy-carbonyl group such as a t-butoxycarbonyl group; and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group. Examples of the protective group for a thiol group include an alkyl group such as a methyl group; an arylmethyl group such as a benzyl group and a triphenylmethyl group; an alkanoyl group such as an acetyl group and a pivaloyl group; and an aroyl group such as a benzoyl group. Examples of the protective group for an imino group include an alkanoyl group such as an acetyl group; an alkoxy-carbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, and a t-butoxycarbonyl group; an arylmethoxycarbonyl group such as a benzyloxycarbonyl group, a para-methoxybenzyloxycarbonyl group, and a para-nitrobenzyloxycarbonyl group; an arylmethyl group such as a benzyl group, a para-methoxybenzyl group, a dimethoxybenzyl group, and a triphenylmethyl group; and an aroyl group such as a benzoyl group.

Deprotection methods of such protective groups are different depending on the chemical properties of a protected reactive group (a hydroxy group, a thiol group, or an imino group) and an employed protective group. For example, an acyl-type protective group such as an alkanoyl group, an alkoxy-carbonyl group, and an aroyl group can be hydrolyzed using a suitable base such as an alkali metal hydroxide including lithium hydroxide, sodium hydroxide, and potassium hydroxide for the deprotection. An alkoxyalkyl-type protective group such as a methoxymethyl group, a methoxyethoxymethyl group, and a tetrahydropyranyl group, a substituted methoxycarbonyl-type protective group such as a t-butoxycarbonyl group and a para-methoxybenzyloxycarbonyl group, and a silyl-type protective group such as a triethylsilyl

151

group and a t-butyl dimethylsilyl group can be removed using a suitable acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid, and trifluoromethanesulfonic acid or a combination of them. The silyl-type protective group can also be removed using a suitable fluorine ion (F) generating reagent such as tetrabutylammonium fluoride and hydrogen fluoride. An arylmethoxycarbonyl group such as a benzyloxycarbonyl group, a para-methoxybenzyloxycarbonyl group, and a para-nitrobenzyloxycarbonyl group and an arylmethyl group such as a benzyl group can be removed by hydrogenolysis using a palladium carbon catalyst. A benzyl group can be removed by Birch reduction using metallic sodium in liquid ammonia. A triphenylmethyl group can be removed using a suitable acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid, and trifluoromethanesulfonic acid or a combination of them. It can also be removed by Birch reduction using metallic sodium in liquid ammonia and removed by hydrogenolysis using a palladium carbon catalyst.

During the production of the compound of Formula (I) of the present invention, when it has a reactive group such as a hydroxy group, an amino group, and a carboxy group, such a group may be properly protected in any reaction step, and the protective group may be removed in a suitable step.

Methods for introducing and removing such protective groups are properly performed depending on the type of a group to be protected or a protective group. For example, such introduction and removal can be performed by methods described in [Protective Groups in Organic Synthesis, edited by Greene et al., the fourth edition (2007), John Wiley & Sons].

Required starting materials are commercially available or can be easily obtained from commercial products by usual production methods in organic chemistry.

Reaction conditions in the production methods are as follows unless otherwise specified. The reaction temperature is in a range from -78°C . to the reflux temperature of a solvent, and the reaction time is a time sufficient for a reaction. Examples of the reaction inert solvent include, but are not limited to, an aromatic hydrocarbon solvent such as toluene, benzene, and xylene; an alcoholic solvent such as methanol, ethanol, and 2-propanol; a polar solvent such as water, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, and 1,3-dimethyl-2-imidazolidinone; a basic solvent such as triethylamine and pyridine; a halogenated solvent such as chloroform, methylene chloride, and 1,2-dichloroethane; an ether solvent such as 1,2-dimethoxyethane, cyclopentyl methyl ether, diethyl ether, tetrahydrofuran, and dioxane; and a mixed solvent of them. Such solvents are properly selected depending on reaction conditions. Examples of the base include, but are not limited to, an inorganic base such as sodium carbonate, potassium carbonate, cesium carbonate,

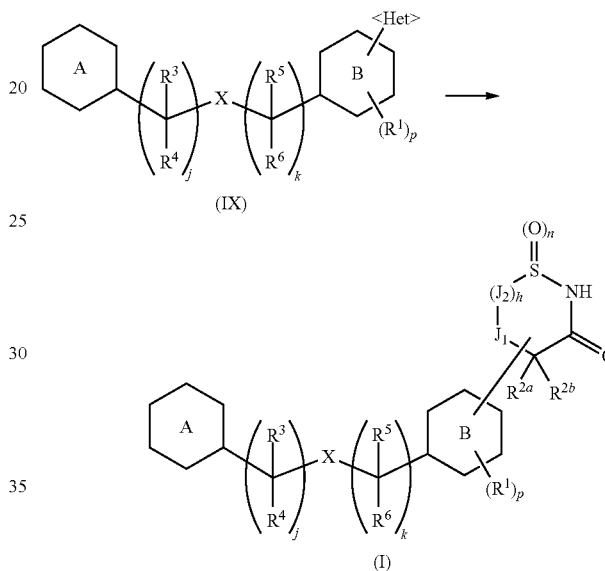
152

sodium hydroxide, potassium hydroxide, and sodium hydride; and an organic base such as triethylamine, N,N-diisopropylethylamine, pyridine, N,N-dialkylaniline, lithium diisopropylamide, and lithium bistrimethylsilylamide.

Examples of the acid include, but are not limited to, a mineral acid such as hydrochloric acid, sulfuric acid, and nitric acid; and an organic acid such as methanesulfonic acid and p-toluenesulfonic acid.

Hereinafter, production methods will be described, but the present invention is not limited to these methods.

The compound of Formula (I) of the present invention can be obtained by a production method suitable for the type of the ring including a saturated amide structure having $-\text{S}(\text{O})\text{n}-\text{NH}-\text{CO}-$. A material compound for the compound is typically shown as Formula (IX).

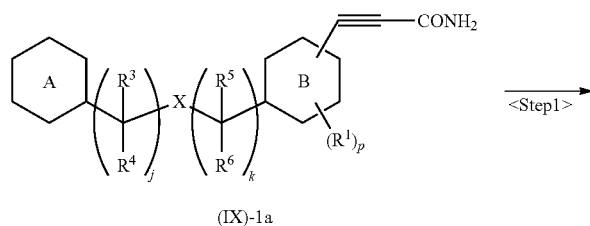


In the formulae in the production method, $\langle\text{Het}\rangle$ generally means a conversion part into the ring structure of a saturated cyclic amide structure that is bonded to the ring B and has $-\text{S}(\text{O})\text{n}-\text{NH}-\text{CO}-$ (n is an integer of 0 to 2, examples of which include W (for example, boronic acid, a boronic ester, and a trifluoroborate salt) and Y (for example, a halogen atom, a nitro group, a protected imino group ($-\text{NP}^1_2$), a formyl group, and an ester group) in the production method, and a molecular chain to form the saturated cyclic amide structure.

(1) Methods for producing the compound of Formula (I)-1a or Formula (I)-2a of the present invention will be described below.

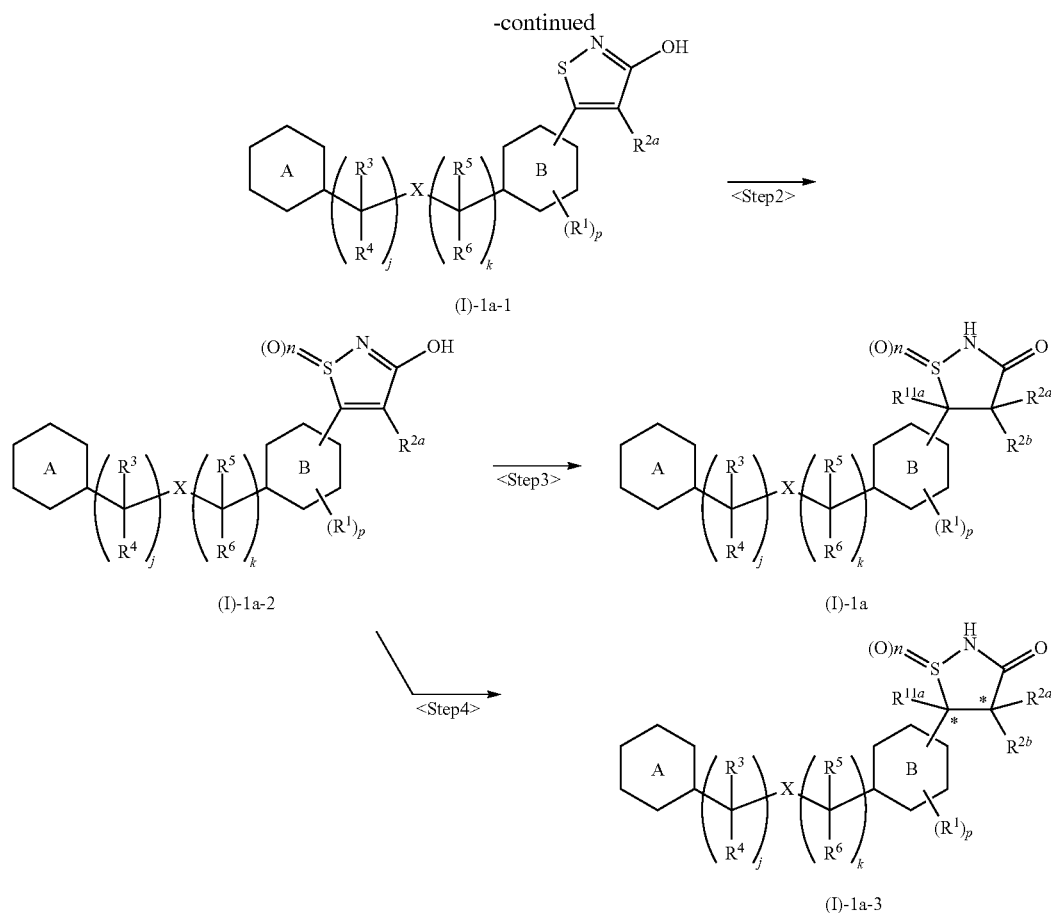
$\langle\text{Production Method A}\rangle$

$\langle\text{When } \text{R}^{2a}=\text{R}^{2b}=\text{H} \text{ and } \text{R}^{1a}=\text{H} \text{ in Formula (I)-1a above}\rangle$



153

154



<Step 1>

The compound of Formula (IX)-1a obtained in (Production Method E) or (Production Method F) described later is subjected to isothiazole ring formation reaction. In accordance with methods known in literatures, for example, the methods described in [Heterocyclic Compounds, New Edition, Applications, pp. 41-57 (2004), Kodansha Ltd.], [Chemische Berichte, vol. 94, p. 2950 (1961)], and [Chemische Berichte, vol. 96, p. 944 (1963)], a compound of (I)-1a-1 can be produced by reacting the compound of Formula (IX)-1a with a thiol (SH) source such as sodium hydrosulfide and hydrogen sulfide gas in a reaction inert solvent such as methanol, ethanol, and water or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent, and then by reacting the obtained thiol adduct in the presence of a halogen such as iodine and bromine and in the presence or absence of a base such as pyridine and potassium carbonate in a reaction inert solvent such as methanol, ethanol, ethyl acetate, and water or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 2>

The sulfur atom in the compound of Formula (I)-1a-1 is oxidized. In accordance with methods known in literatures, for example, the method described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 20, Organic Synthesis V, Oxidation Reaction, pp. 276-280 (1992), Maruzen Co., Ltd.], a compound of Formula (I)-1a-2 can be produced by reacting the compound of Formula (I)-1a-1 in the presence of a peracid or a peroxide such as hydrogen peroxide water, m-chloroperbenzoic acid (MCPBA), per-

acetic acid, trifluoroperacetic acid, Oxone (registered trademark) (DuPont), and tert-butylhydroperoxide (TBHP) in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as acetonitrile, methanol, acetone, and water or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent. In the oxidation reaction, selection of an oxidizing agent and suitable selection of equivalent of a reagent, a reaction temperature, a reaction time, a solvent, and the like can produce a sulfoxide (n=1) and a sulfone (n=2) separately. Such sulfoxide and sulfone can be separated by common techniques such as column chromatography.

<Step 3>

The compound of Formula (I)-1a-2 is subjected to reduction. In accordance with methods known in literatures, for example, the method described in [Japan Institute of Heterocyclic Chemistry, vol. 64, pp. 101-120 (2004)], the compound of Formula (I)-1a can be produced by reacting the compound of Formula (I)-1a-2 in the presence of a reducing agent such as lithium tri(sec-butyl)borohydride (L-selectride), potassium tri(sec-butyl)borohydride, lithium borohydride, and Raney nickel (Raney-Ni)-formic acid or a reducing agent such as a hydride of a metal or a metalloid and a complex compound of them in a reaction inert solvent including an ether solvent such as tetrahydrofuran, diethyl ether, and dioxane, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as acetonitrile and metha-

155

nol or in a mixed solvent of them at a temperature from -78°C . to a reflux temperature of the solvent.

<Step 4>

In accordance with methods known in literatures, for example, the method described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 26, Organic Synthesis VIII, Asymmetric Synthesis, Reduction, Sugar, and Labelled Compound, pp. 23-68 (1992), Maruzen Co., Ltd.], the compound of Formula (I)-1a-3 as an optically active compound of Formula (I)-1a can be produced by reaction in the presence of the compound of Formula (I)-1a-2 in the presence of, for example, optically active dichloro[bis(diphenylphosphino)binaphthyl][diphenylethylenediamine] ruthenium and a basic reagent such as potassium hydroxide and potassium t-butoxide in a hydrogen gas atmosphere using 2-propanol as a solvent at a temperature from room temperature to a reflux temperature of the solvent. Alternatively, the compound of Formula (I)-1a-3 as an optically active compound can be produced by reaction in the presence of a transition-metal complex such as chlorotris(triphenylphosphine)rhodium(I), a reagent such as optically active 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and a hydrogen source such as hydrogen and formic acid-triethylamine using a solvent such as ethanol at a temperature from room temperature to a reflux temperature of the solvent.

In the production methods below, when an isothiazole ring is subjected to reduction, a corresponding optically active compound can be obtained by the reduction in accordance with <Step 4> in <Production Method A>.

The compounds of Formula (II)-1a and Formula (III)-1a above are included in the compound of Formula (I)-1a in

156

(Production Method A) and can be produced by a similar production method. In Formula (II-B), Formula (II-C), Formula (IV-1), Formula (IV-3), Formula (IV-4), Formula (V), Formula (V-A), Formula (VI), Formula (VI-A), Formula (I)-B1, and Formula (I)-B2 above, the compound having Formula (B-Het)-1a is also included in the compound of Formula (I)-1a and can be produced by a similar production method to (Production Method A). These compounds of Formula (I)-1a are included in the compound of Formula (I).

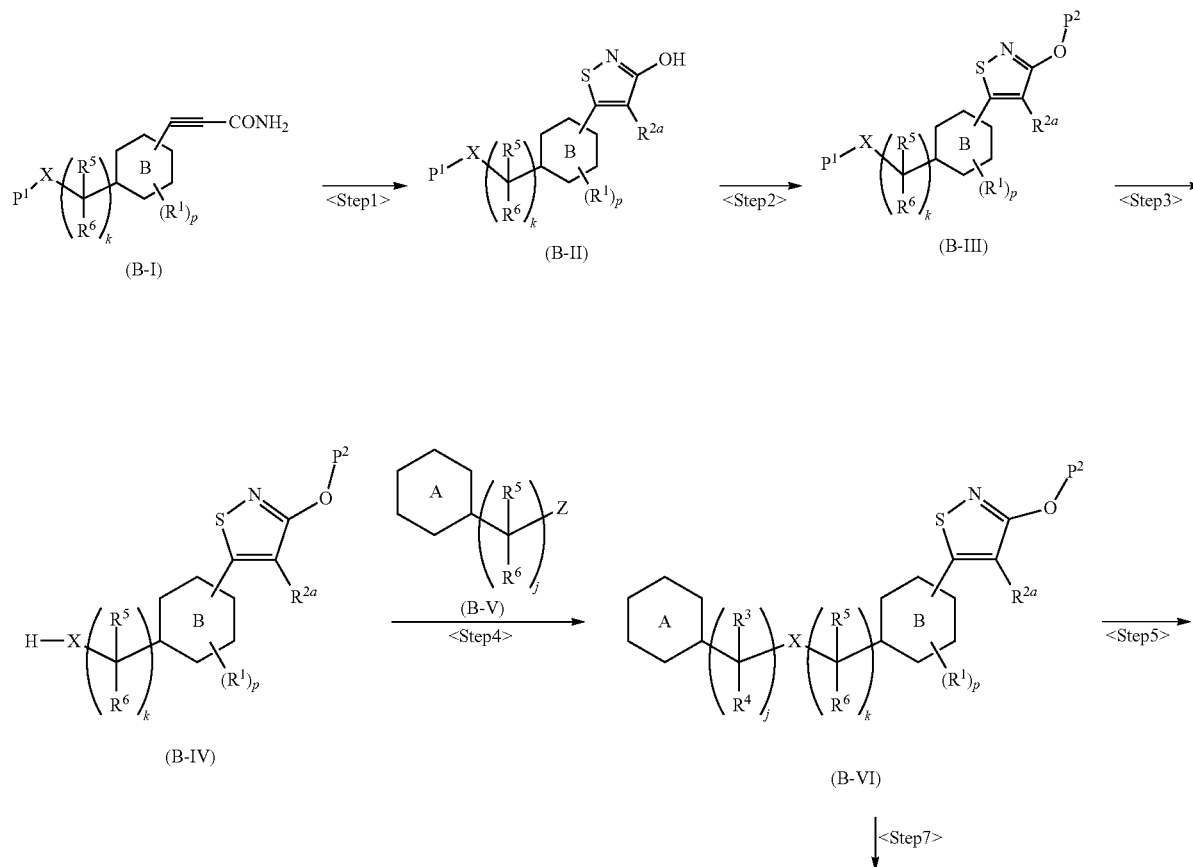
Similarly, in the production methods in (Production Method B) or later, the compounds of Formula (II)-1a and Formula (III)-1a above and the compounds having Formula (B-Het)-1a in Formula (II-B), Formula (II-C), Formula (IV-1), Formula (IV-3), Formula (IV-4), Formula (V), Formula (V-A), Formula (VI), Formula (VI-A), Formula (I)-B1, and Formula (I)-B2 above are included in the compound of Formula (I)-1a and can be produced by a similar production method, and these compounds of Formula (I)-1a are included in the compound of Formula (I).

When $n=0$ in (Production Method A), a compound can be produced without the oxidation step in <Step 2>.

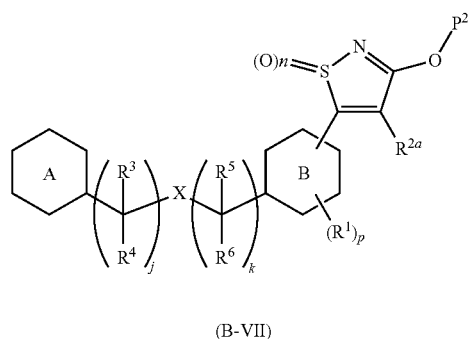
Similarly, in the production methods in (Production Method B) or later, it should be understood that when n is not specified to 0, 1, or 2, an oxide (a sulfoxide or a sulfone derivative) in which $n=1$ or 2 can be produced in accordance with the oxidation reaction in <Step 2> in (Production Method A) in the oxidation step shown in each reaction scheme or a compound (a sulfenamide derivative) in which $n=0$ can be produced without the oxidation step.

<Production Method B>

<When $R^{2a}=R^{2b}=H$ and $R^{11a}=H$ in Formula (I)-1a above>

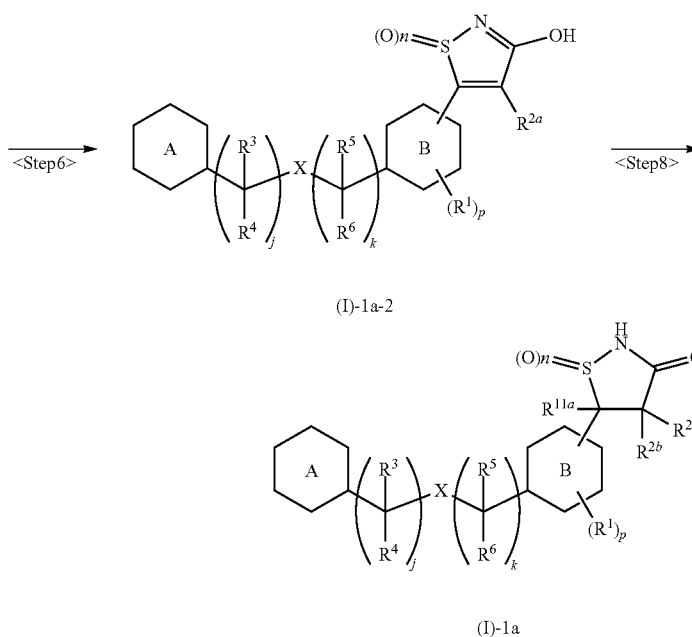


157



-continued

158



<Step 1>

A compound of Formula (B-I) is subjected to isothiazole ring formation reaction. A compound of Formula (B-II) can be produced by reacting the compound of Formula (B-I) (it is known in the art or can be easily produced from a known compound as described later in (Production Method E) and is a properly protected compound) in a similar manner to that in <Step 1> in (Production Method A).

<Step 2>

The compound of Formula (B-II) is protected with a protective group P^2 . A compound of Formula (B-III) can be produced by causing the compound of Formula (B-II) to react with the protective group P^2 by a method suitable for the type of the protective group.

<Step 3>

The protective group P^1 in the compound of Formula (B-III) is deprotected. A compound of Formula (B-IV) can be produced by deprotecting the protective group P^1 in the compound of Formula (B-III) by a method suitable for the type of the protective group.

<Step 4>

The compound of Formula (B-IV) is subjected to substitution reaction with a compound of Formula (B-V).

<When Z=halogen, methanesulfonyloxy Group, or p-toluenesulfonyloxy group>

In accordance with methods known in literatures, for example, the methods described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 20, Organic Synthesis II, Alcohol and Amine, pp. 187-200 and 284-292 (1992), Maruzen Co., Ltd.] and [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 20, Organic Synthesis VI, Hetero Element- or Main Group Metal Element-Containing Compound, pp. 319-350 (1992), Maruzen Co., Ltd.], a compound of Formula (B-VI) can be produced by substitution reaction of the compound of Formula (B-IV) in the presence of the compound of Formula (B-V) in the presence or absence of a base such as triethylamine, pyridine, sodium hydride, sodium hydroxide, and

potassium carbonate in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<When Z=hydroxy group, $X \neq NR^7$, and $k=0$ >

In accordance with methods known in literatures, for example, the method described in [*Tetrahedron*, vol. 67 (10), pp. 3140-3149 (2011)], a compound of Formula (B-VI) can be produced by reacting the compound of Formula (B-IV) in the presence of the compound of Formula (B-V) in the presence of a base such as potassium tert-butoxide and a catalyst such as copper acetate in a reaction inert solvent including an ether solvent such as diethyl ether, tetrahydrofuran, and 1,4-dioxane and an aromatic hydrocarbon solvent such as toluene and benzene or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<When Z=hydroxy group, X=nitrogen atom, and $k=0$ >

In accordance with methods known in literatures, for example, the methods described in [WO 2010/143733 pamphlet, p. 71, [0179]: Step 2 in Reaction scheme 1], [*Tetrahedron Letters*, vol. 36, pp. 63733-6374 (1995)], and [*Tetrahedron Letters*, vol. 38, pp. 5831-5834 (1997)], a compound of Formula (B-VI) can be produced by Mitsunobu reaction of the compound of Formula (B-IV) in the presence of the compound of Formula (B-V) in the presence of an organophosphorus compound such as triphenylphosphine and an azo compound such as an azodicarboxylic acid ester and azodicarboxylic amide in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

The compound of Formula (B-V) used in the step is known in the art or can be produced from a corresponding known

159

compound in accordance with methods known in literatures as described later in (Production Method J), (Production Method J-1), (Production Method J-2), (Production Method J-3), (Production Method J-4), (Production Method J-5), and (Production Method J-6). For example, it can be produced from a corresponding compound in accordance with the methods described in [WO 2005/063729 pamphlet, Reference Examples 2 and 3 and the like], [WO 2005/086661 pamphlet, Example 18 and the like], [WO 2008/001931 pamphlet, Reaction Scheme 2, Reference Examples 15-19, and the like], [WO 2009/039943 pamphlet, pp. 51-52], [WO 2009/054423 pamphlet, Production Examples 12, 24, 37, and the like], [WO 2010/085525 pamphlet, Examples 2-5, 3-3, 4-4, and the like], and [WO 2010/091176 pamphlet, Examples 1-3 and the like]. Examples of the compound include compounds that are obtained by properly protecting the compounds in Example 25-5 and the like.

The compound that is shown as Formula (I) in WO 2009/039943 pamphlet and that has a similar formula to Formula (A)-IX in the present application is represented by Formula III described in WO 2009/039943 pamphlet, p. 52 as Formula (B-V), and the compound is reacted under the condition of <When Z≠hydroxy group> above to produce the compound of Formula (B-VI) (X=nitrogen atom).

<Step 5>

The sulfur atom in the compound of Formula (B-VI) is oxidized. A compound of Formula (B-VII) can be produced by causing the reaction of the compound of Formula (B-VI) in a similar manner to that in <Step 2> in (Production Method A).

<Step 6>

The protective group P² in the compound of Formula (B-VII) is deprotected. A compound of Formula (I)-1a-2 can be produced by deprotecting the protective group P² in the compound of Formula (B-VII) by a method suitable for the type of the protective group.

<Step 7>

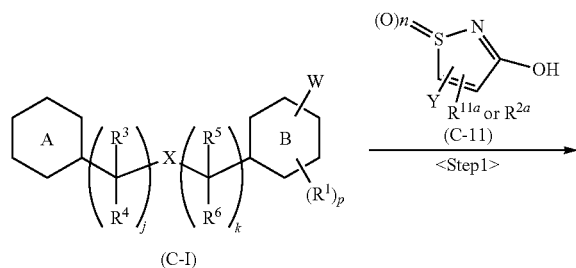
The compound of Formula (B-VI) is simultaneously subjected to oxidation of the sulfur atom and deprotection. When the protective group of P² is a protective group capable of being deprotected by a common oxidation method, a compound of Formula (I)-1a-2 can be produced by reacting the compound of Formula (B-VI) in a similar manner to that in <Step 2> in (Production Method A).

<Step 8>

The compound of Formula (I)-1a-2 is subjected to reduction. The compound of Formula (I)-1a can be produced by causing the reaction of the compound of Formula (I)-1a-2 in a similar manner to that in <Step 3> in (Production Method A).

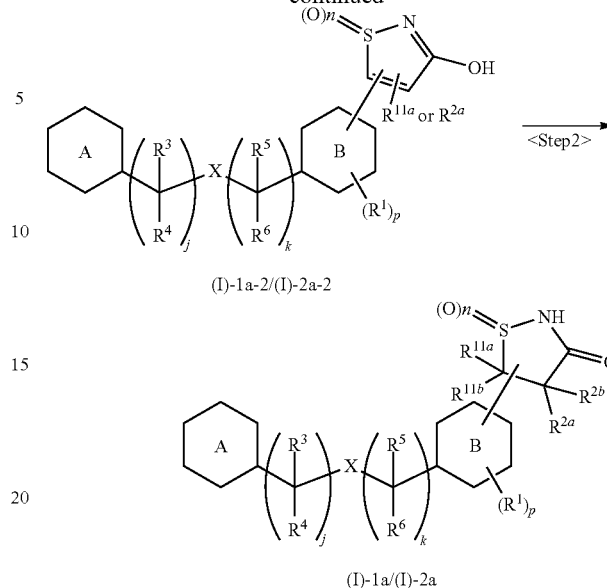
<Production Method C>

<When R^{2b}=H and R^{11b}=H in Formula (I)-1a or Formula (I)-2a above>



160

-continued



<Step 1>

A compound of Formula (C-I) obtained in (Production Method H), (Production Method H-1), (Production Method H-2), or (Production Method H-3) described later is subjected to substitution reaction with a compound of Formula (C-II) (Formula (G-III)a or Formula (I-I)) obtained in (Production Method I) described later. In accordance with methods known in literatures, for example, the methods described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fifth edition, vol. 18, Synthesis of Organic Compound VI, Organic Synthesis Using Metal, pp. 327-352 (2004), Maruzen Co., Ltd.] and [*Journal of Medicinal Chemistry*, vol. 48 (20), pp. 6326-6339 (2005)], a compound of Formula (I)-1a-2/Formula (I)-2a-2 can be produced by reacting the compounds of Formula (C-I) and Formula (C-II) in the presence of three reagents of a palladium catalyst, a phosphine reagent or an alkylammonium halide reagent, and a base reagent using a reaction inert solvent such as toluene, xylene, N,N-dimethylformamide, and N,N-dimethylacetamide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent. Examples of the palladium catalyst include palladium(II) acetate, tetrakis triphenylphosphine palladium, tris(dibenzylideneacetone)dipalladium, bis(dibenzylideneacetone)palladium, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II). Examples of the phosphine reagent include triphenylphosphine, tris(tert-butyl)phosphine, tris(o-tolyl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2',4',6'-trisopropylbiphenyl, and dicyclohexylphosphino-2',4',6'-trisopropylbiphenyl (Xphos). Examples of the base reagent include sodium carbonate, cesium carbonate, potassium carbonate, triethylamine, N,N-diisopropylethylamine, and potassium phosphate. In the reaction above, in place of the phosphine reagent, an alkylammonium halide reagent such as tetramethylammonium chloride and tetrabutylammonium chloride may be used.

Formula (C-II) used in this step is a compound of Formula (G-III)a described later when n=0 and is a compound of Formula (I-I) described later when n≠0.

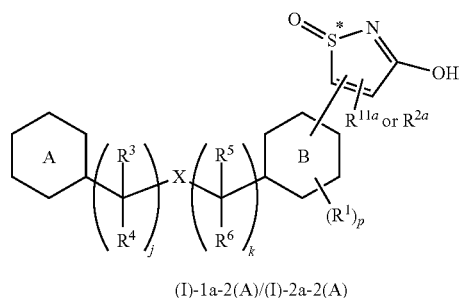
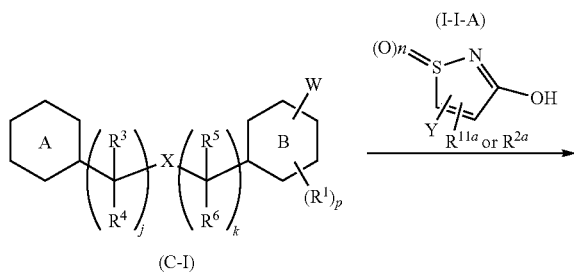
<Step 2>

The compound of Formula (I)-1a-2/Formula (I)-2a-2 is subjected to reduction.

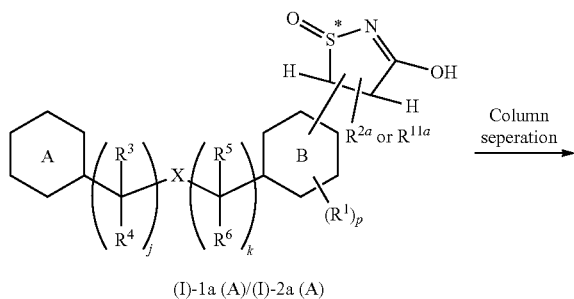
161

The compound of Formula (I)-1a/Formula (I)-2a can be produced by reacting the compound of Formula (I)-1a-2/Formula (I)-2a-2 in a similar manner to that in <Step 3> in (Production Method A).

In the present specification, when $n=1$ in Formula (I)-1a-2/Formula (I)-2a-2 and Formula (I)-1a/Formula (I)-2a above, Formula (I)-1a-2/Formula (I)-2a-2 and Formula (I)-1a/Formula (I)-2a include optical isomers. A compound derived from an enantiomer A (1-1-A) that has a shorter column elution time when optically active Formula (I-I) obtained in (Production Method I) described later is separated by a chiral column is represented by Formula (I)-1a-2 (A)/Formula (I)-2a-2 (A).

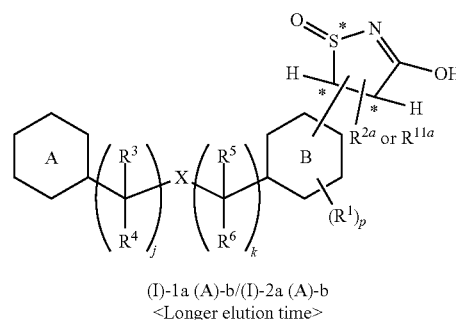
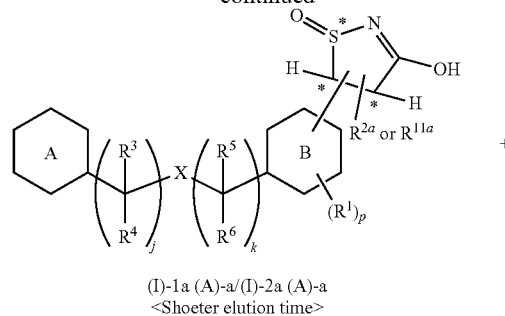


Isomers (diastereomers) of Formula (I)-1a (A)/Formula (I)-2a (A) that are obtained by reduction of the compound in a similar manner to that in <Step 3> in (Production Method A) can be separated through optical resolution using chiral column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques.



162

-continued



For example, each diastereomer can be obtained using preparative chromatography as in Step 2 in Example 7 described later. In the present invention, in the preparative chromatography of a mixture of the diastereoisomers, a diastereomer having a shorter elution time is represented as a, while a diastereomer having a longer elution time is represented as b, and the diastereomers are correspondingly represented by Formula (I)-1a (A)-a/Formula (I)-2a (A)-a and Formula (I)-1a (A)-b/Formula (I)-2a (A)-b. In the present specification, the diastereomers are expressed as a compound name (A)-a and a compound name (A)-b for a compound name.

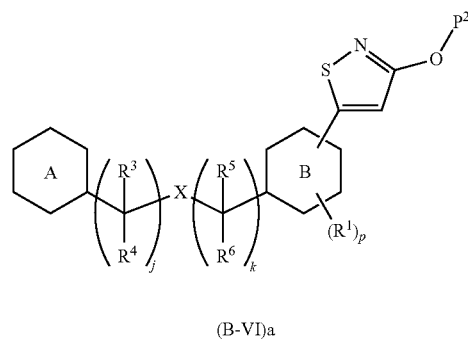
A compound obtained from an enantiomer (B) (1-1-B) having a longer elution time when Formula (I-I) is separated by chiral column resolution is represented as Formula (I)-1a-2 (B)/Formula (I)-2a-2 (B). A compound of Formula (I)-1a (B)/Formula (I)-2a (B) that is obtained by reduction using the compound also includes isomers (diastereomers), which are similarly represented by Formula (I)-1a (B)-a/Formula (I)-2a (B)-a and Formula (I)-1a (B)-b/Formula (I)-2a (B)-b. The diastereomers are expressed as a compound name (B)-a and a compound name (B)-b for a compound name.

In the present specification, when $n=2$ in Formula (I)-1a/Formula (I)-2a above, Formula (I)-1a/Formula (I)-2a includes optical isomers. The isomers can be separated through optical resolution using chiral column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques.

<Production Method D>

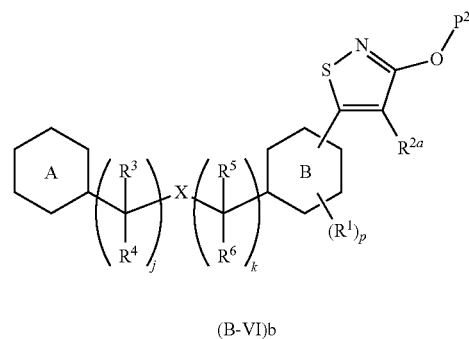
<When $R^{2a} \neq H$, $R^{2b} = H$, and $R^{11a} = H$ in Formula (I)-1a above>

163

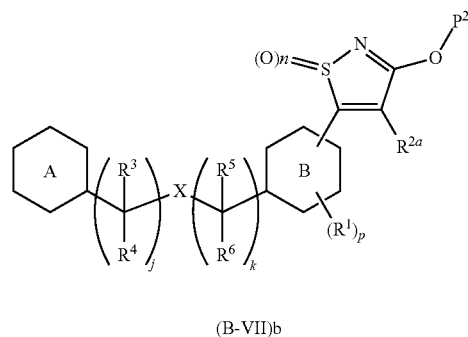


<Step1>

164

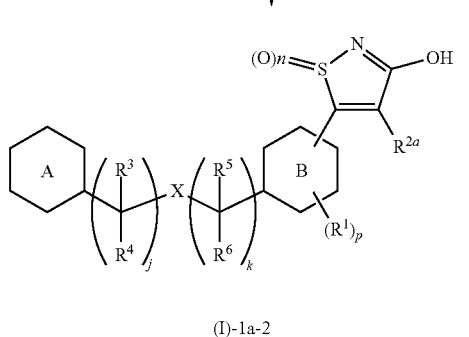


<Step2>

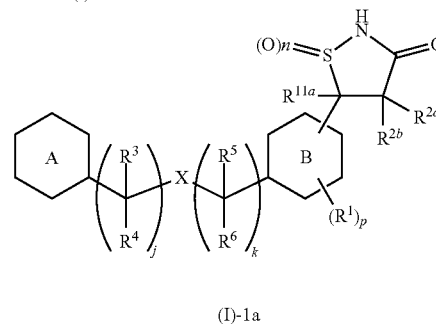


<Step3>

<Step4>



<Step5>



<Step 1>

The compound of Formula (B-VI)a obtained in <Step 4> in (Production Method B) above is subjected to substitution reaction on the isothiazole ring.

<When R^{2a}=halogen atom>

In accordance with methods known in literatures, for example, the method described in [Organic And Biomolecular Chemistry, vol. 5 (3), pp. 643-471 (2007)], a compound of Formula (B-VI)b can be produced by halogenation reaction of the compound of Formula (B-VI)a in the presence of a corresponding halogenating agent such as N-fluorodibenzene-sulfonimide, N-chlorosuccinimide, N-bromosuccinimide, and N-iodosuccinimide in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from -78° C. to a reflux temperature of the solvent.

<When R^{2a}=cyano group>

In accordance with methods known in literatures, for example, the method described in [Tetrahedron Letters, vol. 40 (47), pp. 8193-8195 (1999)], a compound of Formula

(B-VI)b can be produced by reacting the compound of Formula (B-VI)b (R^{2a}=I, Br) obtained in <When R^{2a}=halogen atom> in <Step 1> in (Production Method D) in the presence of a corresponding cyanating agent such as zinc cyanide and potassium ferrocyanide in the presence of a palladium catalyst such as palladium(II) acetate, tetrakis triphenylphosphine palladium, tris(dibenzylideneacetone)dipalladium, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), a phosphine reagent such as triphenylphosphine, tris (tert-butyl)phosphine, and tris(o-tolyl)phosphine, and an organic or inorganic base such as triethylamine, N,N-diisopropylethylamine, and potassium phosphate using a reaction inert solvent such as toluene, xylene, N,N-dimethylformamide, and N,N-dimethylacetamide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent. It can also be produced in a similar method using tetramethylammonium chloride, tetrabutylammonium chloride, or the like in place of the phosphine reagent.

<Step 2>

The sulfur atom in the compound of Formula (B-VI)b is oxidized. A compound of Formula (B-VII)b can be produced by causing the reaction of the compound of Formula (B-VI)b in a similar manner to that in <Step 2> in (Production Method A).

165

<Step 3>

The protective group P² in the compound of Formula (B-VII)b is deprotected. A compound of Formula (I)-1a-2 can be produced by reacting the compound of Formula (B-VII)b in a similar manner to that in <Step 6> in (Production Method B).

<Step 4>

The compound of Formula (B-VI)b is simultaneously subjected to oxidation and deprotection of the protective group P². A compound of Formula (I)-1a-2 can be produced by reacting the compound of Formula (B-VI)b in a similar manner to that in <Step 7> in (Production Method B).

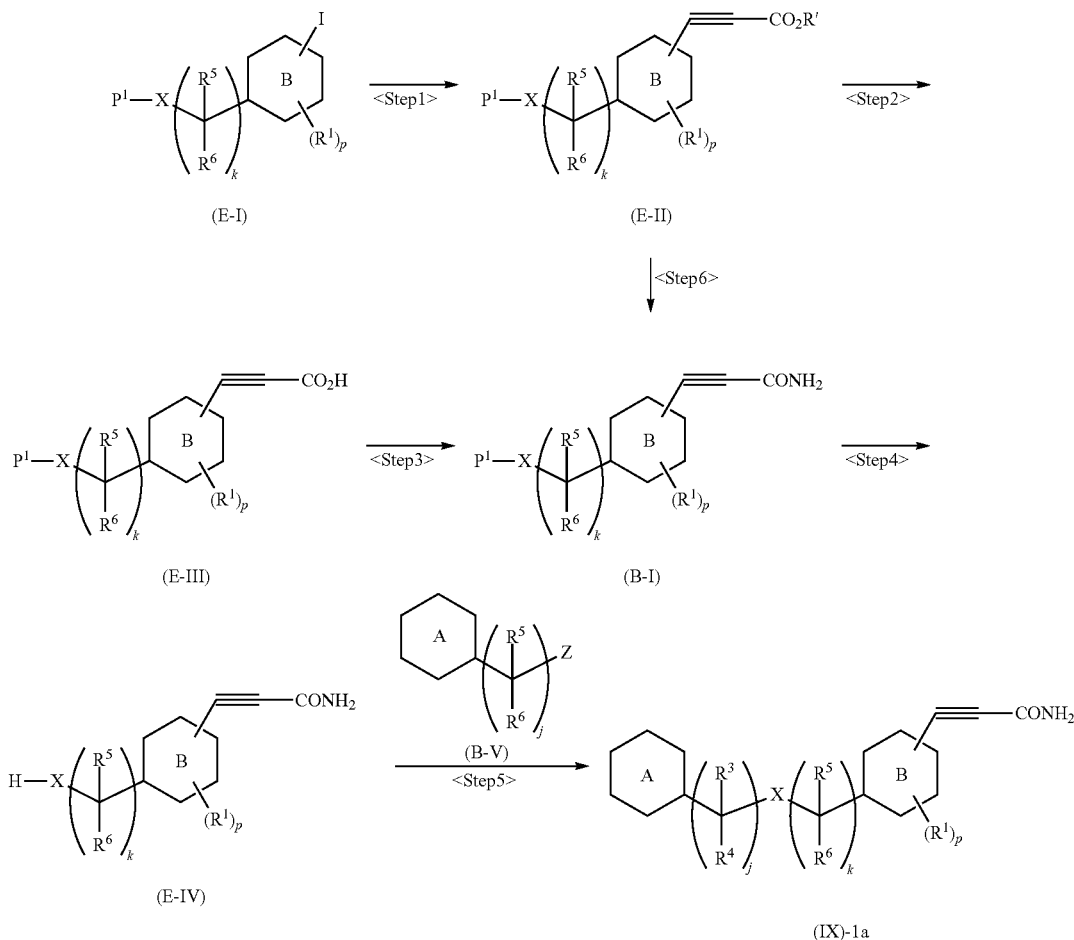
<Step 5>

The compound of Formula (I)-1a-2 is subjected to reduction. The compound of Formula (I)-1a can be produced by causing the reaction of the compound of Formula (I)-1a-2 in a similar manner to that in <Step 3> in (Production Method A).

(2) Next, methods for producing the compounds of Formula (IX)-1a, Formula (B-I), and Formula (B-II) will be described.

The compounds of Formula (IX)-1a and Formula (B-I) can be produced by the methods below.

<Production Method E>



166

perimental Chemistry Course), the fourth edition, vol. 19, Organic Synthesis I, Hydrocarbon and Halogenated Compounds, pp. 318-335 (1992), Maruzen Co., Ltd.] and [WO 2008/066131 pamphlet, Reference Example 1], a compound of Formula (E-II) can be produced by reacting the compound of Formula (E-I), which is known in the art or can be easily produced from a known compound, in the presence of a corresponding propiolic acid ester such as methyl propiolate and ethyl propiolate and copper(II) oxide using a reaction inert solvent such as toluene, xylene, N,N-dimethylformamide, and N,N-dimethylacetamide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

The compound of Formula (E-II) can also be produced by reaction in the presence of an ortho ester of a corresponding propiolic acid such as 3,3,3-triethoxypropyne or a corresponding propiolic acid ester such as methyl propiolate and ethyl propiolate in the presence of copper(I) iodide or zinc bromide in the presence of a palladium catalyst such as palladium(II) acetate, tetrakis triphenylphosphine palladium, tris(dibenzylideneacetone)dipalladium, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), a phosphine reagent such as triphenylphosphine, tris(tert-butyl)phos-

<Step 1>

A compound of Formula (E-I) is subjected to alkynylation. In accordance with methods known in literatures, for example, the methods described in [*Jikken Kagaku Koza* (Ex-

phine, and tris(o-tolyl)phosphine, and an organic or inorganic base such as triethylamine, N,N-diisopropylethylamine, potassium phosphate, and potassium carbonate using a reaction inert solvent such as toluene, xylene, N,N-dimethylfor-

167

amide, and N,N-dimethylacetamide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 2>

The compound of Formula (E-II) is hydrolyzed. In accordance with methods known in literatures, for example, the method described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 22, Organic Synthesis IV, Acid, Amino Acid, and Peptide, pp. 1-43 (1992), Maruzen Co., Ltd.], a compound of Formula (E-III) can be produced by reacting the compound of Formula (E-II) in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, and potassium carbonate using a reaction inert solvent such as water, methanol, ethanol, 2-propanol, N,N-dimethylformamide, 1,4-dioxane, and tetrahydrofuran or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 3>

The compound of Formula (E-III) is subjected to amidation reaction. In accordance with methods known in literatures, for example, the method described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 22, Organic Synthesis IV, Acid, Amino Acid, and Peptide, pp. 191-309 (1992), Maruzen Co., Ltd.], a compound of Formula (B-I) can be produced by reacting the compound of Formula (E-III) with aqueous ammonia or ammonia gas in the presence of a condensing agent such as 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSC-HCl), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (CIP), and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, a polar solvent such as N,N-dimethylformamide, or an alcoholic solvent such as methanol, ethanol, and 2-propanol or in a mixed solvent of them in the presence or absence of a base such as triethy-

168

lamine and pyridine at a temperature from 0° C. to a reflux temperature of the solvent. When the compound of Formula (E-III) is converted into an acid chloride, in accordance with the methods described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 22, Organic Synthesis IV, Acid, Amino Acid, and Peptide, pp. 144-146 (1992), Maruzen Co., Ltd.] and the like, the compound of Formula (B-I) can be produced by reacting the acid chloride in the presence of a base such as triethylamine and pyridine in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 4>

The protective group P¹ in the compound of Formula (B-I) is deprotected. A compound of Formula (E-IV) can be produced by reacting the compound of Formula (B-I) in a similar manner to that in <Step 3> in (Production Method B).

<Step 5>

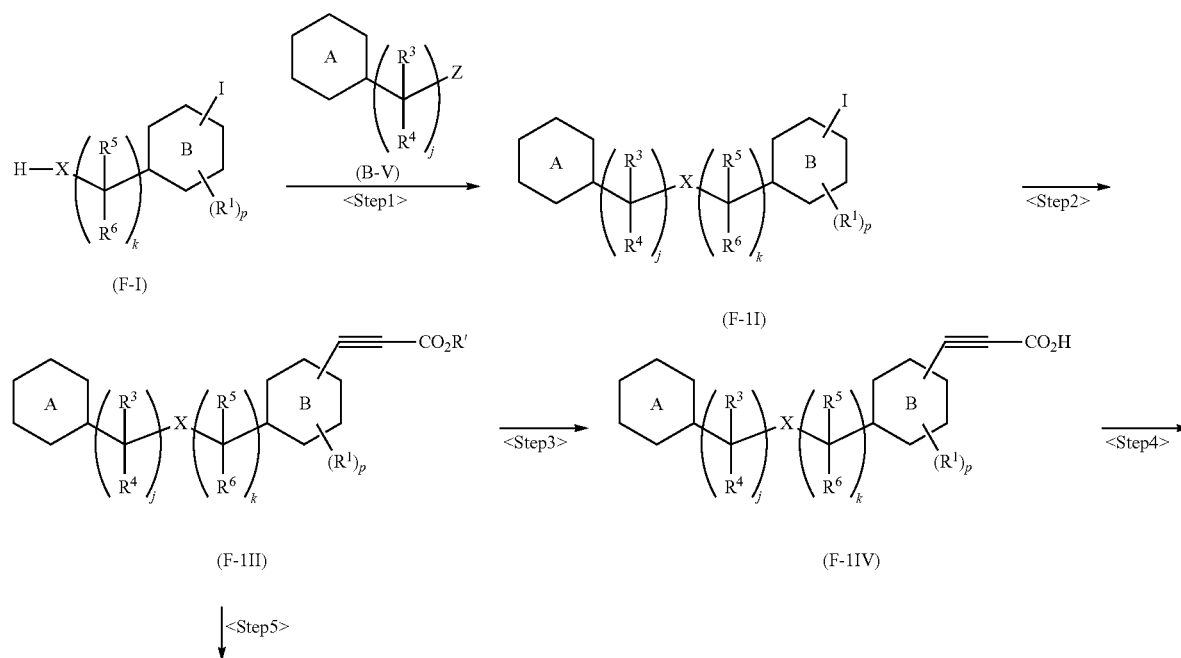
The compound of Formula (E-IV) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (IX)-1a can be produced by causing the compound of Formula (E-IV) to react with the compound of Formula (B-V) in a similar manner to that in <Step 4> in (Production Method B).

<Step 6>

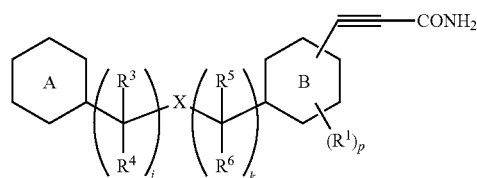
The compound of Formula (B-I) can also be produced from the compound of Formula (E-II). Namely, in accordance with methods known in literatures, for example, the method described in [*Tetrahedron*, vol. 61 (48), pp. 11333-11344 (2001)], the compound of Formula (E-II) can be produced by reaction in the presence of ammonia using a reaction inert solvent such as water, methanol, ethanol, 2-propanol, N,N-dimethylformamide, 1,4-dioxane, and tetrahydrofuran or in a mixed solvent of them at a temperature from -78° C. to a reflux temperature of the solvent.

The compound of Formula (IX)-1a can also be produced by the following method.

<Production Method F>



169



(IX)-1a

<Step 1>

A compound of Formula (F-I) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (F-II) can be produced by reacting the compound of Formula (F-I), which is known in the art or can be easily produced from a known compound, with the compound of Formula (B-V) in a similar manner to that in <Step 4> in (Production Method B).

<Step 2>

The compound of Formula (F-II) is subjected to alkylation. A compound of Formula (F-III) can be produced by causing the reaction of the compound of Formula (F-II) in a similar manner to that in <Step 1> in (Production Method E).

<Step 3>

The compound of Formula (F-III) is hydrolyzed. A compound of Formula (F-IV) can be produced by causing the reaction of the compound of Formula (F-III) in a similar manner to that in <Step 2> in (Production Method E).

<Step 4>

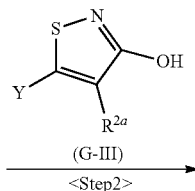
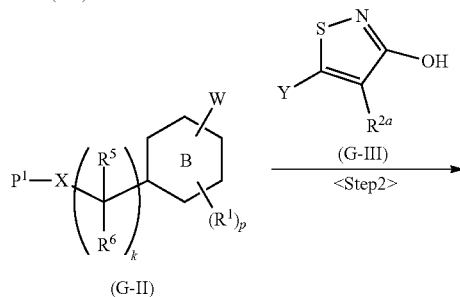
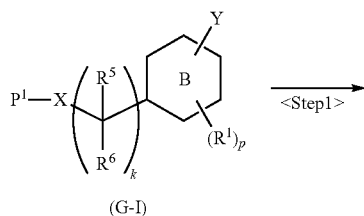
The compound of Formula (F-IV) is subjected to amidation reaction. The compound of Formula (IX)-1a can be produced by causing the reaction of the compound of Formula (F-IV) in a similar manner to that in <Step 3> in (Production Method E).

<Step 5>

The compound of Formula (IX)-1a can also be produced from the compound of Formula (F-III) in a similar manner to that in <Step 6> in <Production Method E>.

The compound of Formula (B-II) can also be produced by the method below.

<Production Method G>

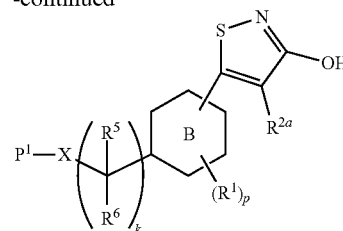


<Step2>

170

-continued

-continued



<Step 1>

A compound of Formula (G-I) is subjected to boration reaction.

<When W=boronic ester>

In accordance with methods known in literatures, for example, the method described in [The Journal of Organic Chemistry, vol. 60, pp. 7508-2665 (1995)], a boronic ester of Formula (G-II) can be produced by reacting the compound of Formula (G-I), which is known in the art or can be easily produced from a known compound, in the presence of a diboronic ester such as bis(pinacolato)diboron and bis(neopentylglycolato)diboron in the presence of a palladium catalyst such as palladium(II) acetate, tetrakis triphenylphosphine palladium, tris(dibenzylideneacetone)dipalladium, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) in the presence or absence of a phosphine reagent such as triphenylphosphine, tris(tert-butyl)phosphine, tris(o-tolyl)phosphine, and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl and an organic or inorganic base such as triethylamine, N,N-diisopropylethylamine, and potassium acetate using a reaction inert solvent such as toluene, N,N-dimethylformamide, dimethyl sulfoxide, and 1,4-dioxane or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent. It can also be produced in a similar method using tetramethylammonium chloride, tetrabutylammonium chloride, or the like in place of the phosphine reagent.

<When W=boronic acid>

In accordance with methods known in literatures, for example, the method described in [Chemische Berichte, vol. 42, p. 3090 (1909)], a boronic acid of Formula (G-I) can be produced by reacting the compound of Formula (G-I) using a reaction inert solvent such as toluene, tetrahydrofuran, and 1,4-dioxane or a mixed solvent of them in the presence of an alkyl lithium such as n-butyllithium and sec-butyllithium, a Grignard reagent such as isopropyl magnesium chloride, or metal magnesium, with a trialkyl borate such as trimethyl borate and triisopropyl borate at a temperature from -78° C. to room temperature, followed by reaction with an acid such as hydrochloric acid and sulfuric acid at a temperature from 0° C. to a reflux temperature of the solvent.

171

<When W=trifluoroborate salt>

In accordance with methods known in literatures, for example, the method described in [Chemical Reviews, vol. 108, pp. 288-325 (2008)], a trifluoroborate salt of Formula (G-II) can be produced by reacting the compound of Formula (G-II) (W=boronic ester or boronic acid) obtained in <When W=boronic ester or boronic acid> in <Step 1> in (Production Method G) in the presence of potassium hydrogen difluoride (KHF₂) using a reaction inert solvent such as methanol, ethanol, and water or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<When W=boronic acid N-methylimino diacetic acid (MIDA) ester>

In accordance with methods known in literatures, for example, the method described in [Journal of Organometallic Chemistry, vol. 307 (1), pp. 1-6 (1986)], a boronic acid N-methylimino diacetic acid (MIDA) ester of Formula (G-II) (W=boronic acid) obtained in <When W=boronic acid> in <Step 1> in (Production Method G) in the presence of N-methyliminodiacetic acid (MIDA) using a reaction inert solvent such as benzene, toluene, xylene, and dimethyl sulfoxide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 2>

The compound of Formula (G-II) is subjected to substitution reaction with a compound of Formula (G-III). The compound of Formula (B-II) can be produced by reacting the compound of Formula (G-II) with the compound of Formula (G-III), which is known in the art or can be easily produced from a known compound, in a similar manner to that in <Step 1> in (Production Method C).

(3) Next, a method for producing the compound of Formula (C-I) will be described.

<Production Method H>

172

<Step 1>

A compound of Formula (H-I) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (H-II) can be produced by reacting the compound of Formula (H-I), which is known in the art or can be easily produced from a known compound, with the compound of Formula (B-V) in a similar manner to that in <Step 4> in (Production Method B).

<Step 2>

The compound of Formula (H-II) is subjected to boration reaction. The compound of Formula (C-I) can be produced by reacting the compound of Formula (H-II) in a similar manner to that in <Step 1> in (Production Method G).

<Step 3>

The compound of Formula (H-I) is subjected to boration reaction. A compound of Formula (H-III) can be produced by reacting the compound of Formula (H-I) in a similar manner to that in <Step 1> in (Production Method G).

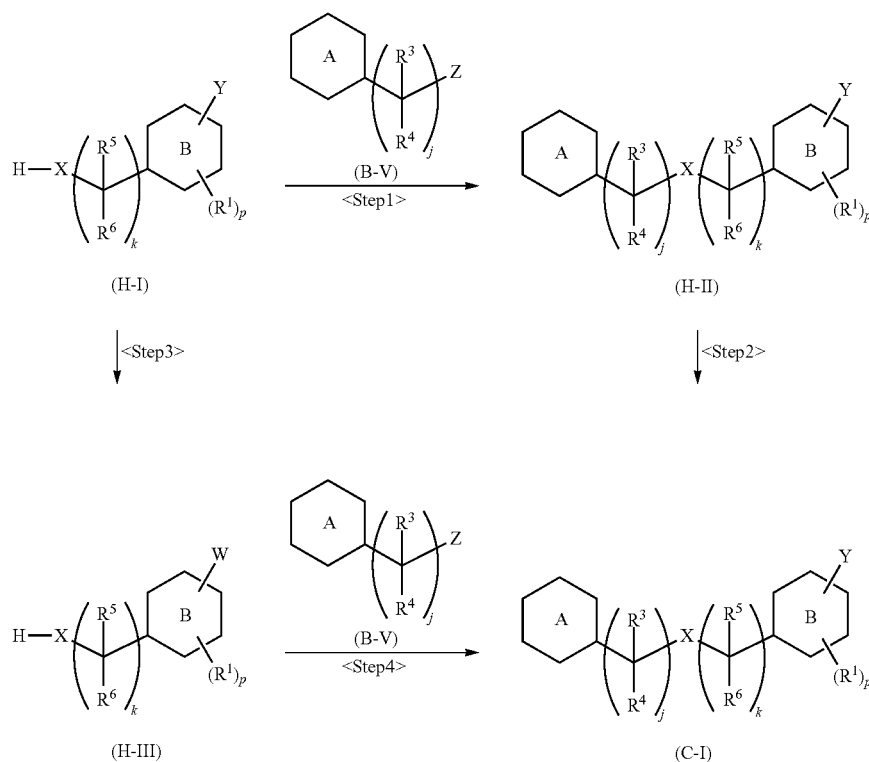
<Step 4>

The compound of Formula (H-III) is subjected to substitution reaction with the compound of Formula (B-V). The compound of Formula (C-I) can be produced by reacting the compound of Formula (H-III) with the compound of Formula (B-V) in a similar manner to that in <Step 4> in (Production Method B).

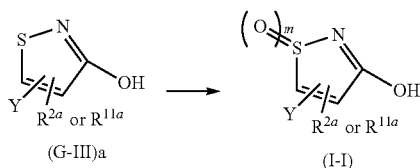
(4) Next, a method for producing the compound of Formula (C-II) will be described.

<Production Method I>

<When n is 1 or 2 in Formula (C-II) above>



173



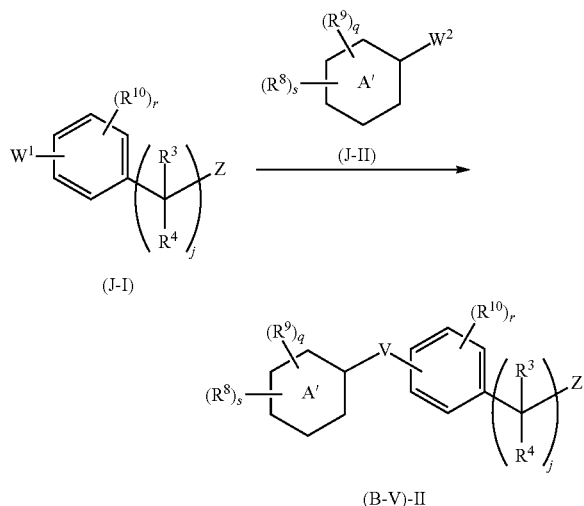
The sulfur atom in a compound of Formula (G-III)a is oxidized. A compound of Formula (I-I) ($m=1$ or 2) can be produced by reacting the compound of Formula (G-III)a, which is known in the art or can be easily produced from a known compound, in a similar manner to that in <Step 2> in (Production Method A).

The compounds of Formula (G-III)a and Formula (I-I) are included in the compound of Formula (C-II).

When m is 1 in Formula (I-I) above, the compound of Formula (I-I) includes optically active isomers. The isomers can be separated through optical resolution using column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques. For example, each enantiomer can be obtained using preparative chromatography as in Step 5 in Example 1 described later.

(5) Hereinafter, the method for producing the compound of Formula (B-V) of the present invention will be described in further detail. As typical examples, methods for producing a compound of Formula (B-V)-II having Partial Structural Formula (A) above and a compound of Formula (B-V)-III having Partial Structural Formula (AA)-1 above will be described.

<Production Method J>



A compound of Formula (J-I) is subjected to substitution reaction on the ring.

<When V=single bond>

A compound of Formula (B-V)-II can be produced by reacting the compound of Formula (J-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (J-II) (W^2 is boronic acid, a boronic ester, or a trifluoroborate salt when W^1 is a halogen atom or a trifluoromethanesulfonyloxy group, and vice versa) in a similar manner to that in <Step 1> in (Production Method C).

174

<When V=oxygen atom>

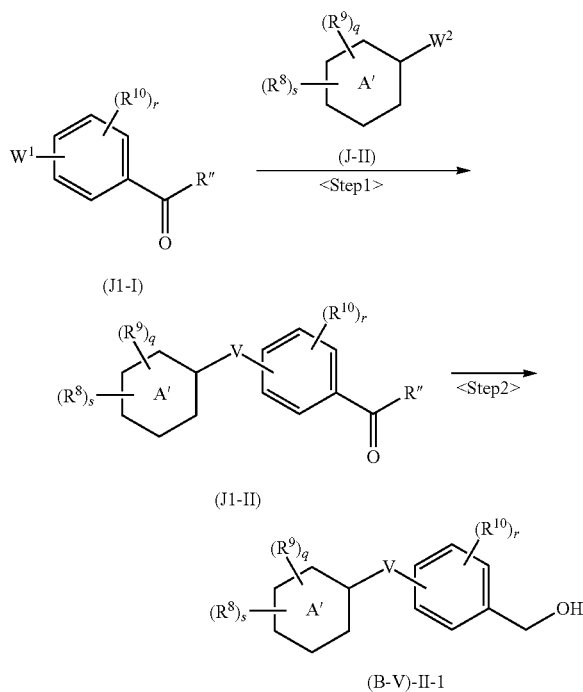
In accordance with methods known in literatures, for example, the method described in [Tetrahedron Letters, vol. 44, pp. 3863-3865 (2003)], the compound of Formula (B-V)-II can be produced by reacting the compound of Formula (J-I) in the presence of a compound of Formula (J-II) (W^2 is boronic acid, a boronic ester, or a trifluoroborate salt when W^1 is a hydroxy group, and vice versa) in the presence of a copper catalyst such as copper(II) acetate and copper(II) trifluoroacetate and a base such as triethylamine, N,N-diisopropylethylamine, and pyridine using a reaction inert solvent such as dichloromethane, 1,4-dioxane, tetrahydrofuran, and N,N-dimethylformamide or a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

When R^8 or R^9 is an electron withdrawing group or the ring A' is heteroaryl, the compound of Formula (B-V)-II can also be produced by reacting a compound of Formula (J-I) (W^1 =hydroxy group) with a compound of Formula (J-II) (W^2 =halogen atom) in a similar manner to that in <Step 4> in (Production Method B).

The compound of Formula (J-II) used in this step is known in the art or can be easily produced from a known compound. Specifically, a halogenated derivative can be produced from a corresponding compound in accordance with methods known in literatures, for example, the methods described in [WO 2005/063729 pamphlet, Reference Example 1 and the like], [WO 2008/001931 pamphlet, <Step 4A> in Reaction Scheme 2, Reference Examples 1, 54, and the like], and [WO 2009/054423 pamphlet, Production Example 37 and the like]. Furthermore, a boronic acid derivative can be produced by boration reaction of the halogenated derivative in a similar manner to that in <Step 1> in (Production Method G).

<Production Method J-1>

<When $j=1$, R^3 , R^4 =H, and Z =OH in Formula (B-V)-II above>



<Step 1>

A compound of Formula (J1-I) is subjected to substitution reaction on the ring.

175

<When V=single bond>

A compound of Formula (J1-II) can be produced by reacting the compound of Formula (J1-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (J-II) in a similar manner to that in <When V=single bond> in (Production Method J).

<When V=oxygen atom>

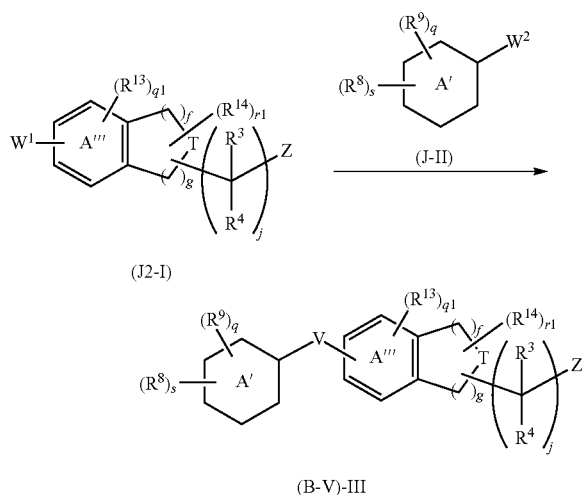
A compound of Formula (J1-II) can be produced by reacting the compound of Formula (J1-I) with a compound of Formula (J-II) in a similar manner to that in <When V=oxygen atom> in (Production Method J).

<Step 2>

The compound of Formula (J1-II) is subjected to reduction. In accordance with methods known in literatures, for example, the method described in [*Jikken Kagaku Koza* (Experimental Chemistry Course), the fourth edition, vol. 26, Organic Synthesis VIII, Asymmetric Synthesis, Reduction, Sugar, and Labelled Compound, pp. 234-245 (1992), Maruzen Co., Ltd.], the compound of Formula (B-V)-II-1 can be produced by reacting the compound of Formula (J1-II) in the presence of sodium borohydride (when R''=H), diisobutyl aluminum hydride (DIBALH), lithium aluminum hydride (LAH), lithium triethoxyaluminum hydride (when R''=C₁₋₆ alkoxy group), borane-tetrahydrofuran (BH₃-THF), borane-dimethyl sulfide (BH₃-Me₂S) (when R''=OH), or the like using a reaction inert solvent including an ether solvent such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and 1,4-dioxane, a halogenated solvent such as dichloromethane, chloroform, and 1,2-dichloroethane, or an alcoholic solvent such as methanol and ethanol or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

The compound of Formula (B-V)-II-1 can also be produced from a corresponding compound in accordance with methods known in literatures, for example, the methods described in [WO 2005/063729 pamphlet, Reference Examples 2, 3 and the like], [WO 2008/001931 pamphlet, Reaction Scheme 2, Reference Examples 15-19, and the like], [WO 2008/130514 pamphlet, Method A, Method C, and the like], [WO 2009/048527 pamphlet, Reaction Formulae 5 and 6, Example 66.6, and the like], and [WO 2009/054423 pamphlet, Production Examples 12, 24, 37, and the like].

<Production Method J-2>



A compound of Formula (J2-I) is subjected to substitution reaction on the ring.

176

<When V=Single Bond>

The compound of Formula (B-V)-III can be produced by reacting the compound of Formula (J24), which is known in the art or can be easily produced from a known compound, with a compound of Formula (J-II) in a similar manner to that in <When V=single bond> in (Production Method J).

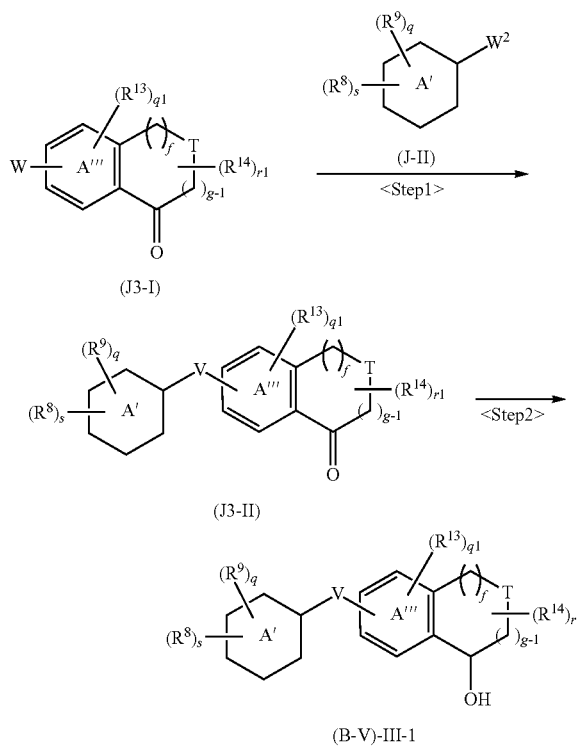
<When V=oxygen atom>

The compound of Formula (B-V)-III can be produced by reacting the compound of Formula (J2-I) with a compound of Formula (J-II) in a similar manner to that in <When V=oxygen atom> in (Production Method J).

The compound of Formula (J2-I) includes optical isomers because a carbon atom in the ring is an asymmetric carbon by bonding the carbon atom to the linker moiety including Z. Such isomers are known in the art or can be easily produced from a known compound. Each enantiomer can be obtained through optical resolution using column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques. For example, the isomers are separated with an optical resolution column, and each absolute configuration can be determined in accordance with [Agric. Biol. Chem., vol. 46 (10), pp. 2579-2585 (1982)]. Furthermore, the enantiomers can be obtained in accordance with the method described in [WO 2009/157418 pamphlet, Example 51 and Example 52]. Each enantiomer of Formula (B-V)-III (for example, compounds in Example 25-5 described later) can be produced using such an enantiomer.

<Production Method J-3>

<When j=0 and Z=OH in Formula (B-V)-III above>



<Step 1>

A compound of Formula (J3-I) is subjected to substitution reaction on the ring.

<When V=single bond>

A compound of Formula (J3-II) can be produced by reacting the compound of Formula (J3-I), which is known in the art or can be easily produced from a known compound, with a

177

compound of Formula (J-II) in a similar manner to that in <When V=single bond> in (Production Method J).

<When V=oxygen atom>

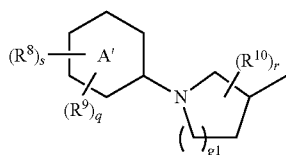
A compound of Formula (J3-II) can be produced by reacting the compound of Formula (J3-I) with a compound of Formula (J-II) in a similar manner to that in <When V=oxygen atom> in (Production Method J).

<Step 2>

The compound of Formula (J3-II) is subjected to reduction. The compound of Formula (B-V)-III-1 can be produced by reacting the compound of Formula (J3-II) with sodium borohydride, diisobutyl aluminum hydride (DIBAH), or lithium aluminum hydride (LAH) in a similar manner to that in <Step 2> in (Production Method J-1).

The compound of Formula (B-V)-III-1 can also be produced from a corresponding compound in accordance with methods known in literatures, for example, the methods described in [WO 2005/063729 pamphlet, Reference Examples 2, 3 and the like], [WO 2008/001931 pamphlet, Reaction Scheme 2, Reference Examples 15-19, and the like], and [WO 2009/054423 pamphlet, Production Examples 12, 24, 37, and the like].

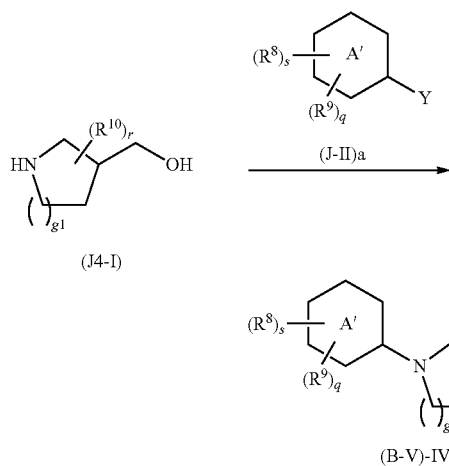
(5-1) As another typical example of the compound of Formula (B-V), a method for producing a compound of Formula (B-V)-IV having Partial Structural Formula (A1)-IV:



will be described.

<Production Method J-4>

<When the ring A is Partial Structural Formula (A1)-IV above, j=1, R³, R⁴=H, and Z=OH in Formula (B-V) above>

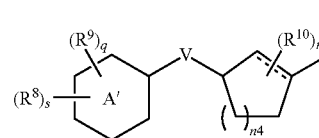


An amino alcohol of Formula (J4-I) is subjected to substitution reaction. In accordance with methods known in literatures, for example, the method described in [WO 2006/021401 pamphlet], the compound of Formula (B-V)-IV can be produced by reacting the compound of Formula (J4-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (J-II)a in the

178

presence of potassium phosphate and copper iodide using a reaction inert solvent including a polar solvent such as dimethylaminoethanol and N,N-dimethylformamide, an ether solvent such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and 1,4-dioxane, or an alcoholic solvent such as methanol and ethanol or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

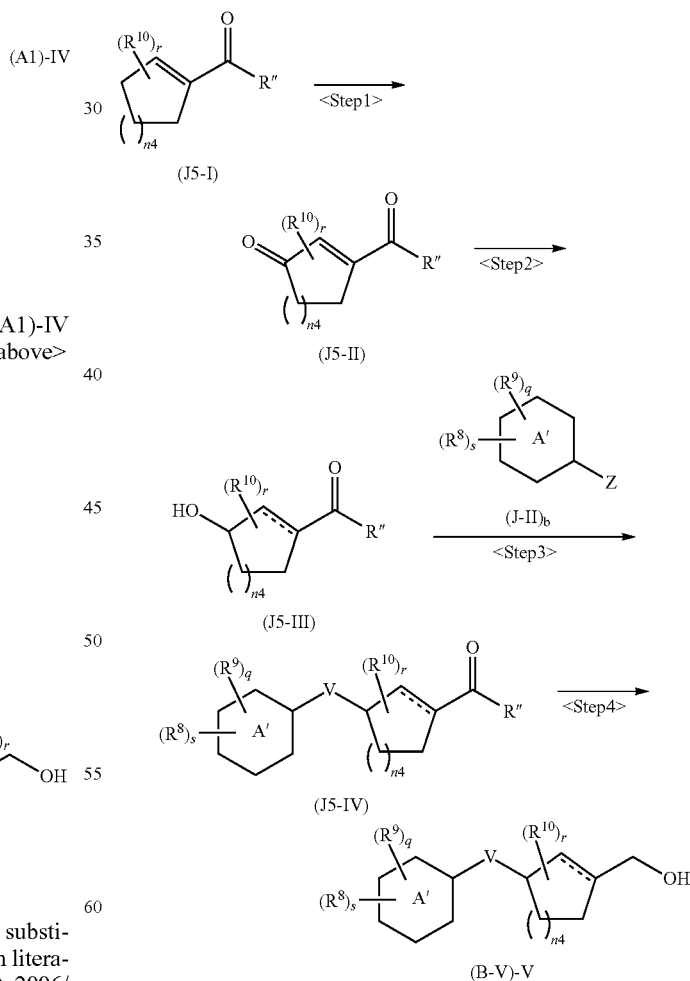
(5-2) As another typical example of the compound of Formula (B-V), a method for producing a compound of Formula (B-V)-V having Partial Structural Formula (AA1)-V:



will be described.

<Production Method J-5>

<When the ring A is Partial Structural Formula (AA1)-V above (When V=an oxygen atom), j=1, R³, R⁴=H, and Z=OH in Formula (B-V) above>



<Step 1>

A compound of Formula (J5-I) [in Formula, Rⁿ is a C₁₋₆ alkoxy group] is oxidized. In accordance with methods

179

known in literatures, for example, the method described in [Journal of Organic Chemistry, vol. 43, pp. 2057 (1978)], a compound of Formula (J5-II) can be produced by reacting the compound of Formula (J5-I), which is known in the art or can be easily produced from a known compound, with chromium trioxide (CrO_3) in the presence of 3,5-dimethylpyrazole using a reaction inert solvent such as methylene chloride, 1,2-dichloroethane, acetonitrile, and benzene or a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

<Step 2>

[When the Ring Structure in Formula (J5-III) has a Double Bond (γ -Hydroxy- α,β -Unsaturated Ester)]

The compound of Formula (J5-II) is subjected to reduction. A compound of Formula (J5-III) can be produced by causing the compound of Formula (J5-II) to react with sodium borohydride and cerium chloride in a similar manner to that in <Step 2> in (Production Method J-1).

[When the Ring Structure in Formula (J5-III) is Saturated (α -Hydroxy- α,β -Saturated Ester)]

The compound of Formula (J5-II) is subjected to reduction. A compound of Formula (J5-III) can be produced by causing the compound of Formula (J5-II) to react with sodium borohydride in a similar manner to that in <Step 2> in (Production Method J-1).

<Step 3>

The compound of Formula (J5-III) is subjected to substitution reaction with a compound of Formula (J-II)b. A compound of Formula (J5-IV) can be produced by reacting the compound of Formula (J-II)b, which is known in the art or can be easily produced from a known compound, with the compound of Formula (J5-III) in a similar manner to that in <Step 4> in (Production Method B).

<Step 4>

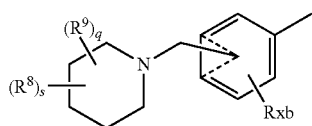
[When the Aliphatic Ring Structure has a Double Bond (γ -Hydroxy- α,β -Unsaturated Ester)]

The compound of Formula (J5-IV) is subjected to reduction. The compound of Formula (B-V)-V can be produced by causing the compound of Formula (J5-IV) to react with diisobutyl aluminum hydride (DIBAH) in a similar manner to that in <Step 2> in (Production Method J-1).

[When the Aliphatic Ring Structure is Saturated (α -Hydroxy- α,β -Saturated Ester)]

The compound of Formula (J5-IV) is subjected to reduction. The compound of Formula (B-V)-V can be produced by reacting the compound of Formula (J5-IV) with lithium aluminum hydride (LAH) or diisobutyl aluminum hydride (DIBAH) in a similar manner to that in <Step 2> in (Production Method J-1).

(5-3) As another typical example of the compound of Formula (B-V), a method for producing a compound of Formula (B-V)-VI having Partial Structural Formula (AA)-VI:

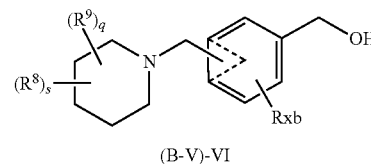
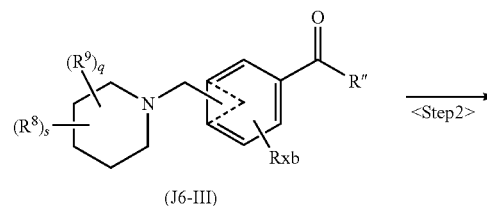
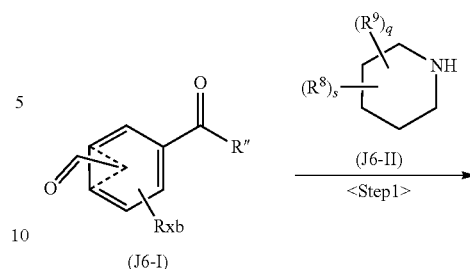


will be described.

<Production Method J-6>

<When the ring A is Partial Structural Formula (AA)-VI above, $j=1$, R^3 , $R^4=\text{H}$, and $Z=\text{OH}$ in Formula (B-V) above>

180



<Step 1>

A compound of Formula (J6-I) [in Formula, R'' is a C_{1-6} alkoxy group] is subjected to reductive amination. In accordance with methods known in literatures, for example, the method described in [The Journal of Organic Chemistry, vol. 61, pp. 3849-3862 (1996)], a compound of Formula (J6-III) can be produced by reacting the compound of Formula (J6-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (J6-II) in the presence of a reducing agent such as sodium triacetoxyborohydride and sodium cyanoborohydride in the presence or absence of a catalytic amount of acetic acid using a reaction inert solvent such as dichloromethane, 1,2-dichloroethane, tetrahydrofuran, acetonitrile, and toluene or a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

<Step 2>

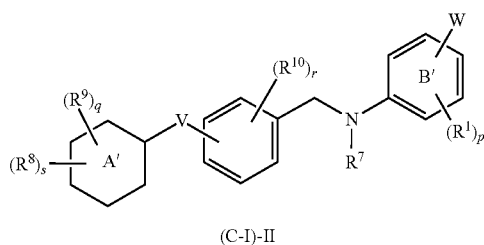
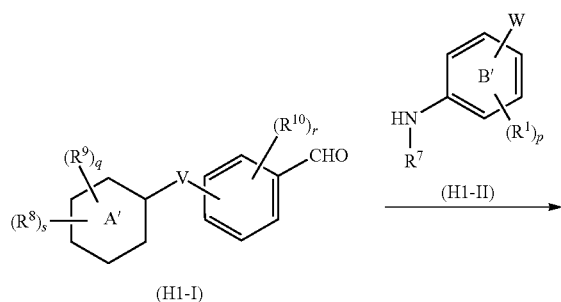
The compound of Formula (J6-III) is subjected to reduction. The compound of Formula (B-V)-VI can be produced by causing the reaction of the compound of Formula (J6-III) in a similar manner to that in <Step 2> in (Production Method J-1).

(3-1) The compound of Formula (C-I) can also be produced by the methods below.

<Production Method H-1>

<When the ring A is Partial Structural Formula (A) above, the ring B is the ring B', $j=1$, $k=0$, R^3 , $R^4=\text{H}$, and $X=\text{NR}^7$ in Formula (C-I) above>

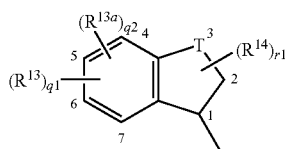
181



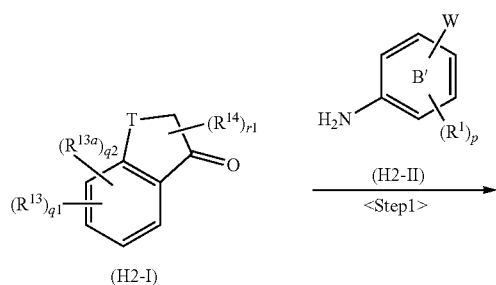
A compound of Formula (H1-I) is subjected to reductive amination. The compound of Formula (C-I)-II can be produced by reacting the compound of Formula (H1-I) (the compound of Formula (H1-I) is included in the compound of Formula (J1-II) and can be easily produced from a known compound as shown in <Step 1> in (Production Method J-1) above) with a compound of Formula (H1-II) (it is known in the art or can be easily produced from a known compound) in a similar manner to that in <Step 1> in (Production Method J-6).

<Production Method H-2>

<When the ring A is Partial Structural Formula (AA1):

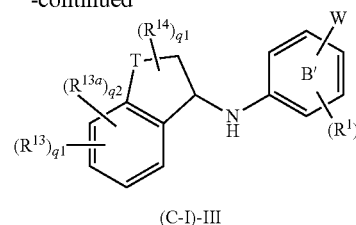


the ring B is the ring B' , $j=0$, and $X=NH$ in Formula (C-I) above>

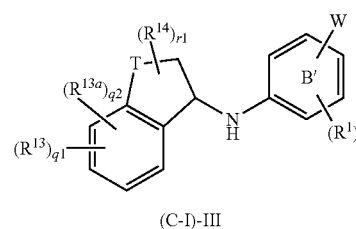
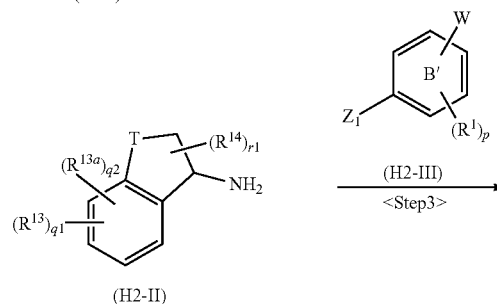
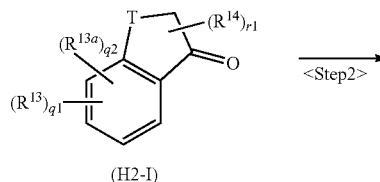


182

-continued



A compound of Formula (H2-I) is subjected to reductive amination. In accordance with methods known in literatures, for example, the method described in [WO 2006/128670 pamphlet], the compound of Formula (C-I)-III can be produced by reacting the compound of Formula (H2-I) (it is known in the art or can be easily produced from a known compound as shown in <Step 1> in (Production Method J-3) above and the like) with a compound of Formula (H2-II) (it is known in the art or can be easily produced from a known compound) (<Step 1>).



The compound of Formula (C-I)-III can also be produced by reacting, in accordance with methods known in literatures, for example, the method described in [WO 2006/085149 pamphlet], the compound of Formula (H2-I) with hydroxylamine hydrochloride to afford an oxime, then by hydrogenating the oxime using hydrogen and Pd-C to produce a compound of Formula (H2-II) (<Step 2>), and by reacting the obtained compound of Formula (H2-II) with a compound of Formula (H2-III) in accordance with methods known in literatures, for example, the method described in [WO 2005/682859 pamphlet or Journal of the American Chemical Society, vol. 128 (29), pp. 9306-9307 (2006)] (<Step 3>). Z_1 in Formula (H2-III) above is halogen, a methanesulfonyloxy group, or a p-toluenesulfonyloxy group in Z above.

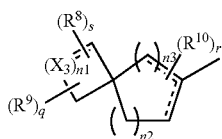
<Step 2> above can be carried out with reference to known reaction conditions for reductive amination, for example, in

183

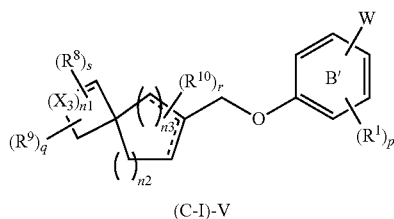
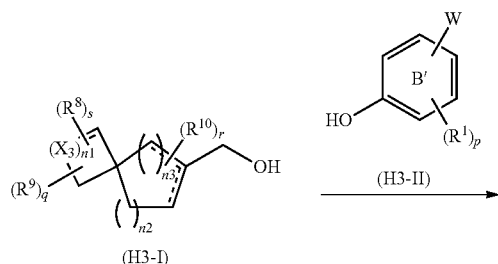
[WO 2006/083454 pamphlet, p. 62, Steps A and B in Preliminary Example] and [WO 2010/143733 pamphlet, Reference Example 68]. <Step 3> above can be carried out in accordance with known reaction conditions for substitution, for example, in [WO 2010/143733 pamphlet, [0184], Step 7].

<Production Method H-3>

<When the ring A is Partial Structural Formula (A)-V:



the ring B is the ring B', j=1, k=0, R³, R⁴=H, and X=oxygen atom in Formula (C-I) above>



A compound of Formula (H3-I) is subjected to substitution reaction with a compound of Formula (H3-II). The compound of Formula (C-I)-V can be produced by reacting the compound of Formula (H3-II), which is known in the art or can be easily produced from a known compound, with the compound of Formula (H3-I) in a similar manner to that in <Step 4> in (Production Method B) or in accordance with the method described in [WO 2009/054479 pamphlet, Step 1 or Step 1' in Production Method A1 (for example, Step 6 in Example 41)]. For example, condensation is carried out in a solvent at room temperature or under heating. Examples of the reagent include 1,1'-(diazocarbonyl)dipiperidine and triphenylphosphine. Examples of the solvent include an ether solvent such as tetrahydrofuran.

The compound of Formula (H3-I) above is known in the art or can be easily produced from a known compound with

184

reference to, for example, [WO 2009/054479 pamphlet, Production Method B, C, D, or the like (paragraphs [0185] to [0264])].

Hereinafter, the methods for producing the compound of Formula (H3-I) of the present invention will be described in further detail.

<Production Method H-4>

<When n₃=1, the broken line adjacent to the carbon atom in the n₃ moiety is a double bond, and the other broken lines are single bonds in Formula (H3-I) above>

(A)-V

15

20

25

30

35

40

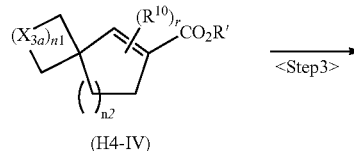
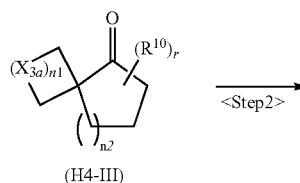
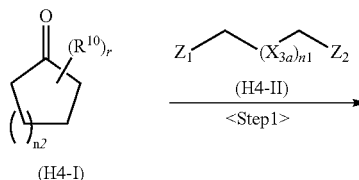
45

50

55

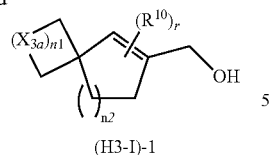
60

65



185

-continued



<Step 1>

A compound of Formula (H4-I) is subjected to substitution reaction with a compound of Formula (H4-II) (each X_{3a} in Formula (H4-II) is independently $—CR_{V1a}R_{V2a}—$ or $—NR_{V3a}—$, each of R_{V1a} , R_{V2a} , and R_{V3a} is independently a hydrogen atom, $—OH$, or $—NH_2$, each definition of Z_1 and Z_2 is the same as that of Z above, and Z_1 and Z_2 are preferably a halogen atom). A compound of Formula (H4-III) can be produced by reacting the compound of Formula (H4-I), which is known in the art or can be easily produced from a known compound, with the compound of Formula (H4-II) in accordance with the method described in [WO 2009/054479 pamphlet, Production Method D1-1 (for example, Step 1 in Example 41 and Step 4 in Example 104)]. For example, the condensation is carried out in a solvent at room temperature or under heating in the presence of a base. Examples of the base include potassium tert-butoxide and sodium hydride. Examples of the solvent include an aromatic hydrocarbon solvent such as toluene.

<Step 2>

A compound of Formula (H4-IV) can be produced from the compound of Formula (H4-III) in accordance with the method described in [WO 2009/054479 pamphlet, Steps 1 to 4 in Production Method C1-1 (for example, Steps 2 to 4 in Example 41)].

<Step 3>

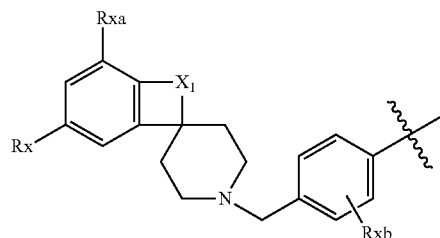
The compound of Formula (H3-I)-1 can be produced from the compound of Formula (H4-IV) in accordance with the method described in [WO 2009/054479 pamphlet, Step 5 in Production Method C1-1 (for example, Step 5 in Example 41)].

186

<Production Method H-5>

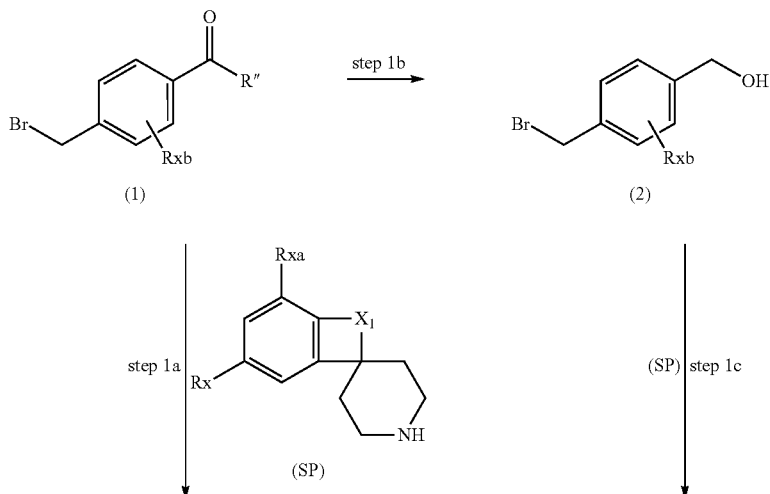
<When the ring A is Partial Structural Formula (A)-VI:

(A)-VI



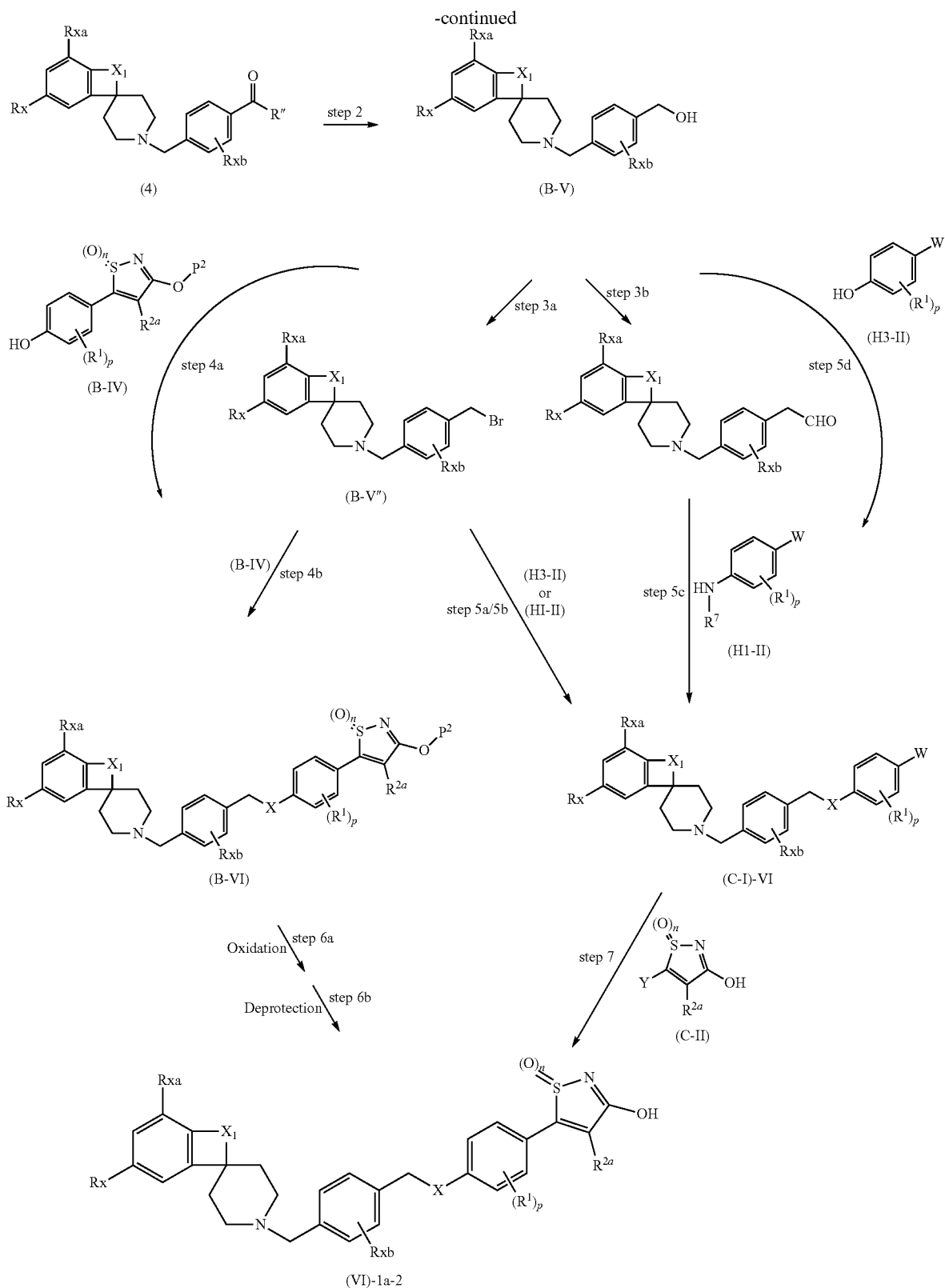
the ring B is a benzene ring, a linker moiety including an isothiazolyl group and X is placed at the p-position, $j=1$, $k=0$, and R^3 , $R^4=H$ in Formula (C-1) above>

As shown in the scheme below, in accordance with Scheme 1 in WO 2011/046851 pamphlet, pp. 8-9, a substituted benzyl bromide of Formula (1) is reacted with a suitable substituted spiroperidine of Formula (SP) or its hydrochloric acid salt or trifluoroacetic acid salt in the presence of a suitable base such as diisopropylethylamine and cesium carbonate to give a compound of Formula (4) in step 1a. The ester is properly reduced in step 2 with diisobutylaluminum hydride, lithium aluminum hydride, sodium borohydride, or the like to give a substituted benzyl alcohol of Formula (B-V). The compound of Formula (B-V) can be properly used in, for example, (Production Method B), (Production Method E), (Production Method F), and (Production Method H) above and (Production Method L) below. The compound of Formula (B-V) can also be obtained by reduction in step 1b instead of step 1a to give a compound of Formula (2), followed by reaction with the compound of Formula (SP) in step 1c in the same manner as in the above.



187

188



Here, the compound of Formula (B-V) is further reacted with a phenol derivative of Formula (B-IV) by Mitsunobu reaction in step 4a in the presence of a suitable phosphine such as triphenylphosphine and triethylphosphine and an

azodicarbonyl such as ADDP or an azodicarboxylate such as DEAD, and then the product is properly oxidized and deprotected in steps 6a and 6b to give a compound of Formula (VI)-1a-2 (X=oxygen atom).

189

Another pathway may be employed. That is, the compound of Formula (B-V) is derived to a benzyl bromide of Formula (B-V') in step 3a with a suitable brominating agent such as phosphorus tribromide, and then the benzyl bromide is reacted with the phenol derivative of Formula (B-IV) above in step 4b to give the compound of Formula (B-VI).

The compound of Formula (B-V') is also reacted with a compound of Formula (H3-II) or a compound of Formula (H1-II) in step 5a/b to give a corresponding compound of Formula (C-I)-VI (X=oxygen atom or —NR₇—). Alternatively, the compound of Formula (C-I)-VI can be derived from the compound of Formula (B-V) by oxidation with a suitable oxidizing agent such as Dess-Martin reagent to give an aldehyde of Formula (5) in step 3b, followed by oxidative amination with a compound of Formula (H1-II) in step 5c. The compound of Formula (C-I)-VI (X=oxygen atom or

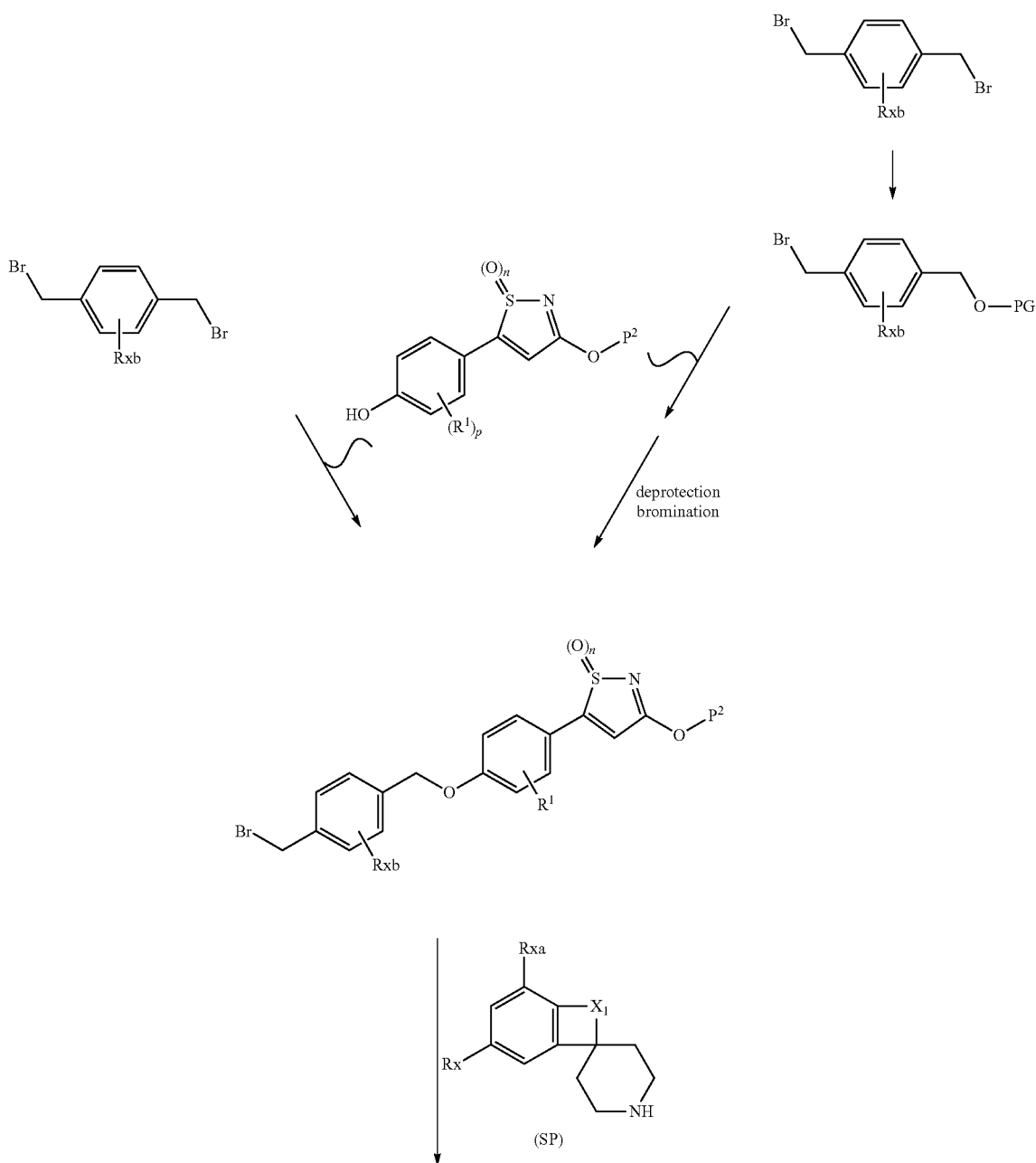
190

—NR₇—) can also be derived from the compound of Formula (B-V) by direct Mitsunobu reaction with a compound of Formula (H3-II) in step 5d.

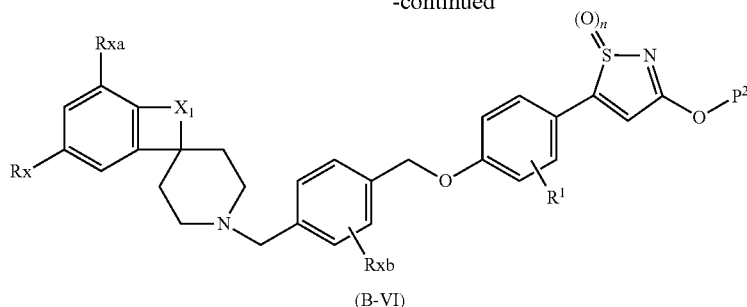
The compound of Formula (C-I)-VI is reacted with a compound of Formula (C-II) in step 7 to give a compound of Formula (VI)-1a-2 (X=oxygen atom or —NR₇—).

A final compound of Formula (VI)-1a can be produced by reduction of the obtained compound of Formula (VI)-1a-2 in a similar manner to that in <Step 3> in (Production Method A).

Through the synthetic route shown below, the compound of Formula (B-VI) can also be obtained using a known or suitable benzyl bromide derivative to give an intermediate, followed by reaction with a substituted spiro piperidine of Formula (SP). Each definition of substituents and reference signs is the same as in the above.



-continued



In particular, a method for producing a compound of Formula (B-V) where X_1 is $-\text{N}(\text{Rz})\text{CH}_2-$ can be with reference to WO 2011/064851 pamphlet, pp. 10-11. In accordance with Scheme II in the literature, a protected piperidine-4-carbaldehyde is reacted with a phenylhydrazine that may be substituted at the 2-position and/or 4-position to give a substituted spiro[indoline-3,4'-piperidine]. The product is, as necessary, further alkylated, and then is deprotected to give the compound of Formula (SP) suited for the present invention.

WO 2011/046851 pamphlet discloses in pp. 29-31, as specific known compounds of Formula (B-V) suitably used for Production Method U of the present invention, (4-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)phenyl)methanol as well as [3-chloro-4-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)phenyl]methanol, [2-methoxy-4-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)phenyl]methanol, [3-fluoro-4-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)phenyl]methanol, [4-(spiro[inden-1,4'-piperidin]-1'-ylmethyl)-3-(trifluoromethyl)phenyl]methanol, [3-chloro-4-[(1-methylspiro[indolin-3,4'-piperidin]-1'-yl)methyl]phenyl]methanol, [4-(spiro[indan-1,4'-piperidin]-1'-ylmethyl)-3-(trifluoromethyl)phenyl]methanol, and [4-(spiro[indan-1,4'-piperidin]-1'-ylmethyl)phenyl]methanol.

As other usable compounds of Formula (B-V'), WO 2011/046851 pamphlet also discloses, in pp. 31-32, corresponding bromomethyl derivatives as Prep No. 56-61.

Hereinbefore, the method for producing a compound substituted with an isothiazole ring at the p position with respect to the hetero atom X has been described. Furthermore, an m-isomer that can be properly obtained or synthesized is used in place of the starting material of Formula (1) or Formula (2) to produce a corresponding compound substituted with the isothiazole ring at the m position with respect to the hetero atom X in a similar manner.

<Production Method H-5a>

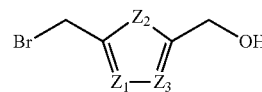
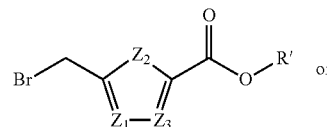
It can be understood that another substituted spiropiperidine of Formula (SP') is used in place of the substituted spiropiperidine of Formula (SP) in each production route in (Production Method H-5) to give each compound of Formula (B-Va), Formula (B-Va'), Formula (C-1)-VIa, Formula (B-VIa), and Formula (VIa)-1a-2 having the moiety of Formula (SP') that replaces the moiety of Formula (SP) in each compound of Formula (B-V), Formula (B-V'), Formula (C-1)-VI, Formula (B-VI), and Formula (VI)-1a-2.

Furthermore, each compound of Formula (B-V), Formula (B-V'), Formula (B-Va), and Formula (B-Va') described in (Production Method H-5) and (Production Method H-5a) can be used as the compound of Formula (B-V) in (Production Method B), (Production Method E), (Production Method F),

or (Production Method H) above, (Production Method L) below, or the like in each step (for example, in <Step 4> in (Production Method B)).

<Production Method H-5b>

In place of the starting material of Formula (1) or Formula (2) used in steps 1a, 1b, and 1c in (Production Method H-5) or (Production Method H-5a), in accordance with the description of scheme I or scheme III in pp. 5 to 10 in WO 2011/066183 pamphlet, a corresponding bromomethyl-heteroaryl-carboxylic acid derivative of Formula (1) or a methyl alcohol of bromomethyl-heteroaryl of Formula (2):

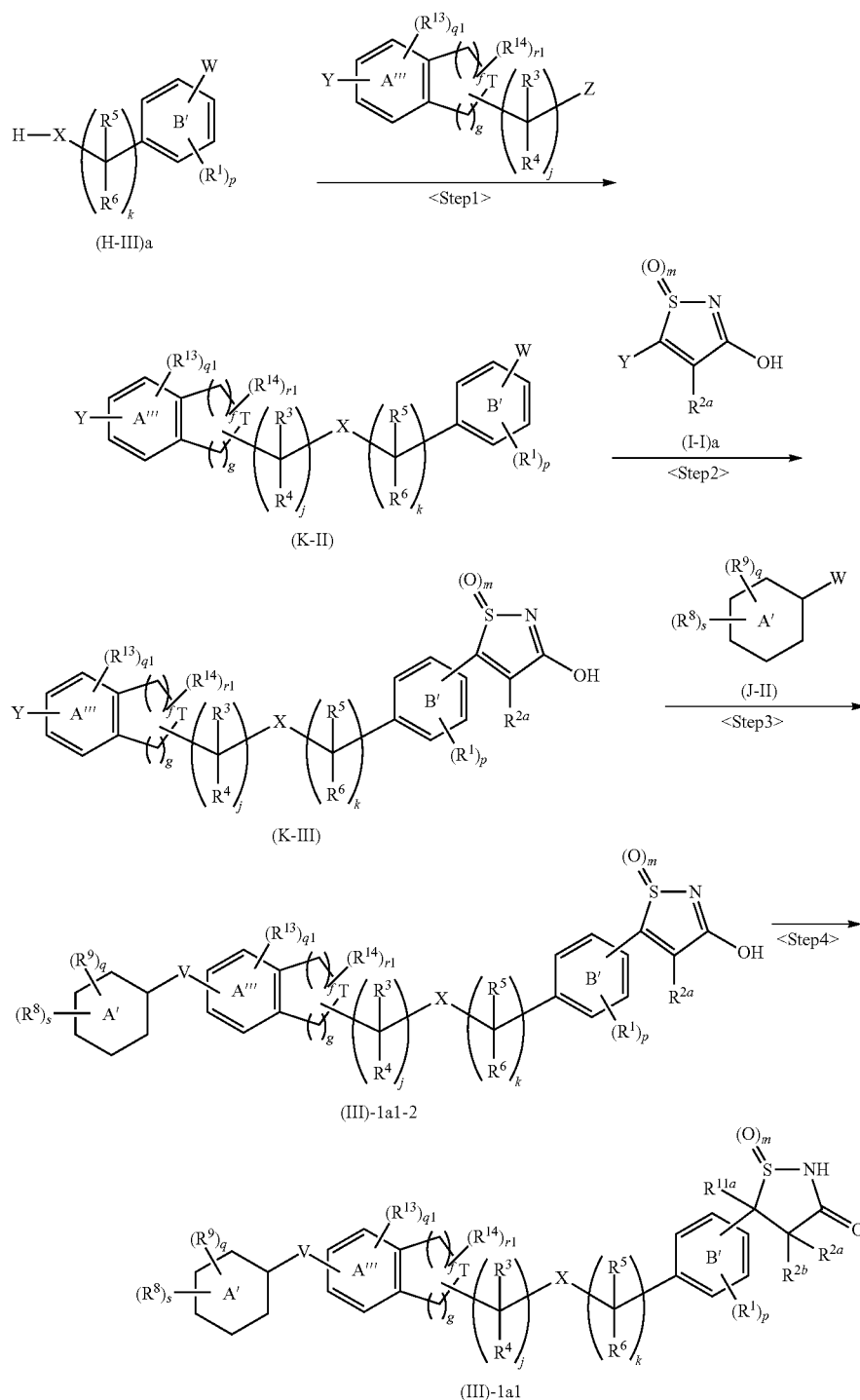


(where each definition of Z_1 , Z_2 , and Z_3 is the same as that in Formula (A2) IV described in the aspect [1-13-e-3]) is used to produce the compound in the aspect [1-13-e-8] or [1-13-e-8a] having a 5-membered heteroaryl in the molecule.

(6) The compound of Formula (I)-1a can also be produced by the methods below.

<Production Method K>

<When the ring A is Partial Structural Formula (AA)-1 above (that is Formula (III)-1a1), $X=\text{oxygen atom}$, $R^{2b}=\text{H}$, and $R^{11a}=\text{H}$ in Formula (I)-1a above>



<Step 1>

A compound of Formula (H-III)a is subjected to substitution reaction with a compound of Formula (K-I). A compound of Formula (K-II) can be produced by reacting the compound of Formula (H-III)a obtained in <Step 3> in (Production Method H) above with the compound of Formula (K-I), which is known in the art or can be easily produced from a known compound, in a similar manner to that in <Step 4> in (Production Method B).

<Step 2>

The compound of Formula (K-II) is subjected to substitution reaction with a compound of Formula (I-I)a. A compound of Formula (K-III) can be produced by reacting the compound of Formula (K-II) with the compound of Formula (I-I)a in a similar manner to that in <Step 1> in (Production Method C).

<Step 3>

The compound of Formula (K-III) is subjected to substitution reaction with a compound of Formula (J-II).

195

<When V=single bond>

A compound of Formula (III)-1a1-2 can be produced by reacting the compound of Formula (K-III) with the compound of Formula (J-II) in a similar manner to that in <Step 1> in (Production Method C).

<When V=oxygen atom>

In accordance with methods known in literatures, for example, the method described in [Tetrahedron Letters, vol. 49, pp. 1851-1855 (2008)], a compound of Formula (III)-1a1-2 can be produced by reacting the compound of Formula (K-III) in the presence of the compound of Formula (J-II) in the presence of a copper catalyst such as copper(I) iodide, copper(I) bromide, copper(I) chloride, and copper(I) oxide, a base such as potassium phosphate, potassium carbonate, and sodium tert-butoxide, and an additive such as 1-butylimidazole, 1-methylimidazole, and 2,2'-bipyridine using a reaction inert solvent such as toluene, xylene, 1,4-dioxane, and N-methylpyrrolidone or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

In accordance with other methods known in literatures, for example, the method described in [Journal of the American Chemical Society, vol. 121, pp. 4369-4378 (1999)], the compound of Formula (III)-1a1-2 can also be produced by reacting the compounds of Formula (K-III) and Formula (J-II) in the presence of a palladium catalyst such as palladium(II) acetate, tetrakis triphenylphosphine palladium, tris(dibenzylideneacetone)dipalladium, bis(dibenzylideneacetone)palladium, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), a phosphine reagent such as (2-biphenyl)di-(tert-butyl)phosphine, 2-di-(tert-butyl)-2'-(N,N-dimethylamino)biphenyl, and 2-dicyclohexyl-2'-(N,N-dimethylamino)biphenyl, and a base such as potassium phosphate, sodium hydride, and sodium tert-butoxide using a reaction inert solvent such as dichloromethane, 1,4-dioxane, tetrahydrofuran, toluene, and N,N-dimethylformamide or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

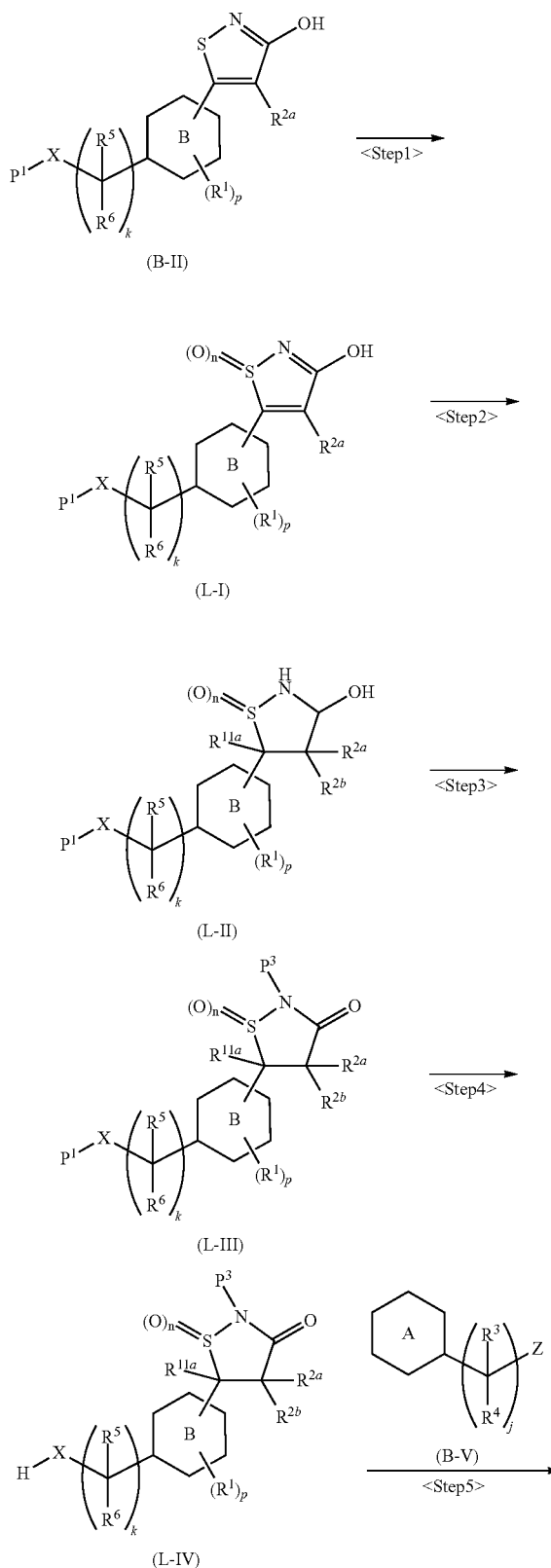
<Step 4>

The compound of Formula (III)-1a1-2 is subjected to reduction. The compound of Formula (III)-1a1 can be produced by causing the reaction of the compound of Formula (III)-1a1-2 in a similar manner to that in <Step 3> in (Production Method A).

The compound of Formula (K-I) includes optical isomers because a carbon atom is an asymmetric carbon by bonding the carbon atom to Z. As with Formula (J2-I) above, such isomers are known in the art or can be easily produced from a known compound. Each enantiomer can be obtained through optical resolution using column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques (for example, (1S)-4-bromo-2,3-dihydro-1H-inden-1-ol). Each enantiomer of Formula (K-II), Formula (K-III), Formula (III)-1a1-2, and Formula (III)-1a1 (for example, compounds in Example 23-3, Example 23-4, Example 23-5, and Example 23 described later) can be produced using such an enantiomer.

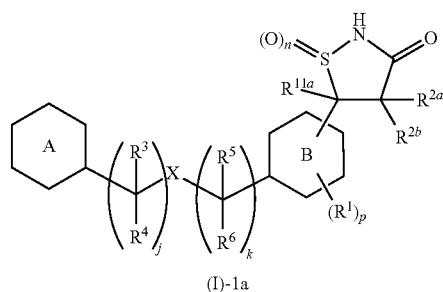
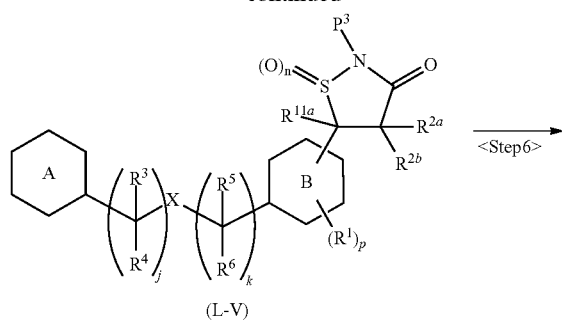
196

<Production Method L>

<When R^{2b}=H and R^{11a}=H in Formula (I)-1a>

197

-continued



<Step 1>

The sulfur atom of a compound of Formula (B-II) is oxidized. A compound of Formula (L-I) can be produced by reacting the compound of Formula (B-II) in a similar manner to that in <Step 2> in (Production Method A).

<Step 2>

The compound of Formula (L-I) is subjected to reduction. A compound of Formula (L-II) can be produced by reacting the compound of Formula (L-I) in a similar manner to that in <Step 3> in (Production Method A).

<Step 3>

The compound of Formula (L-III) is protected with a protective group P^3 . A compound of Formula (L-III) can be produced by causing the reaction of the compound of Formula (L-II) in a similar manner to that in <Step 2> in (Production Method B).

<Step 4>

The protective group P^1 in the compound of Formula (L-III) is deprotected. A compound of Formula (L-IV) can be produced by causing the reaction of the compound of Formula (L-III) in a similar manner to that in <Step 3> in (Production Method B).

<Step 5>

The compound of Formula (L-IV) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (L-V) can be produced by causing the reaction of the compound of Formula (L-IV) in a similar manner to that in <Step 4> in (Production Method B).

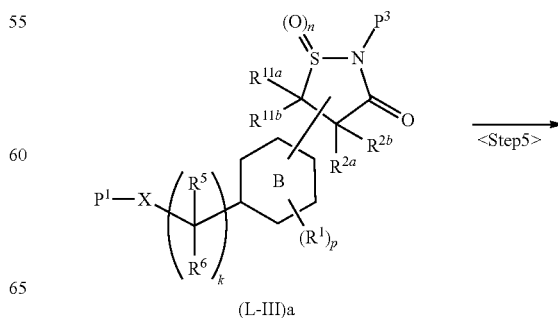
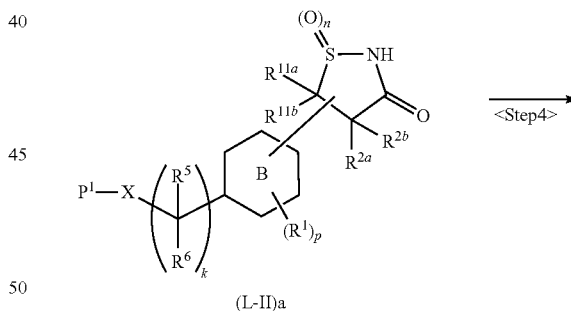
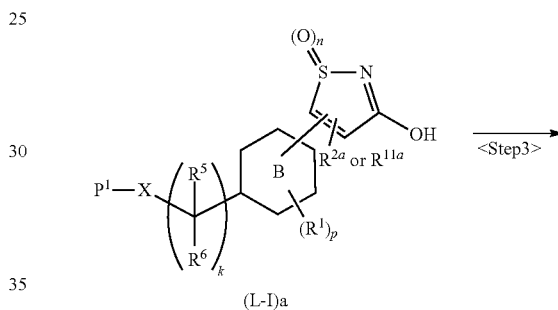
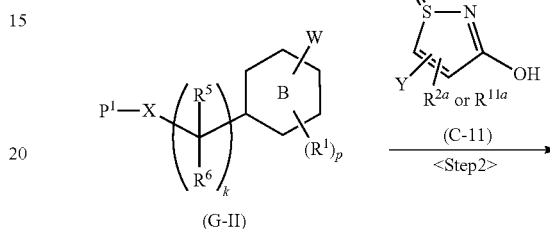
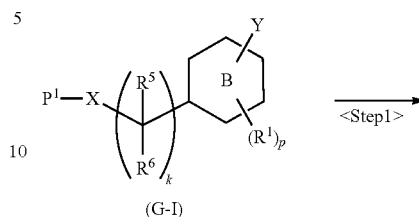
<Step 6>

The protective group P^3 in the compound of Formula (L-V) is deprotected. The compound of Formula (I)-1a can be produced by causing the reaction of the compound of Formula (L-V) in a similar manner to that in <Step 3> in (Production Method B).

198

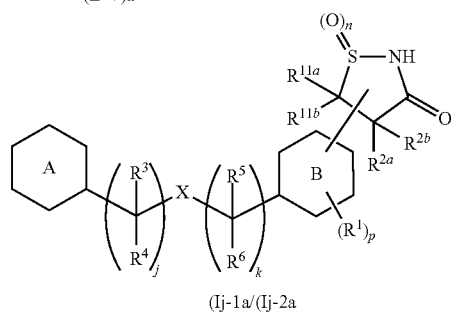
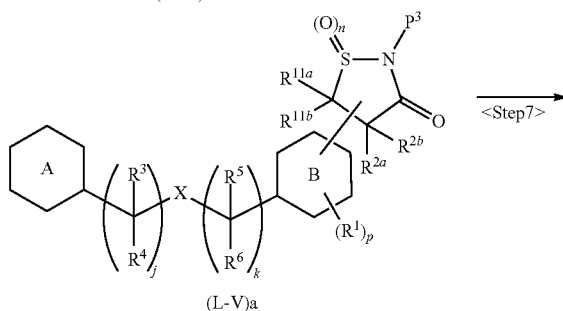
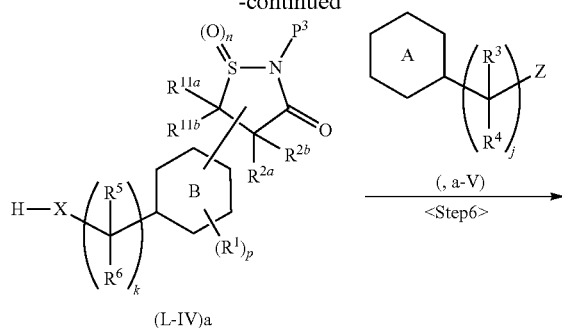
<Production Method L-1>

<When X=oxygen atom in Formula (I) above>



199

-continued



200

<Step 1>

A compound of Formula (G-II) can be produced by reaction in a similar manner to that in <Step 1> in (Production Method G).

<Step 2>

A compound of Formula (L-I)a can be produced by reaction in a similar manner to that in <Step 2> in (Production Method G).

<Step 3>

A compound of Formula (L-II)a can be produced by reac-
 15 tion in a similar manner to that in <Step 2> in (Production
 Method L).

<Step 4>

20 A compound of Formula (L-III)a can be produced by reaction in a similar manner to that in <Step 3> in (Production Method L).

<Step 5>

25 A compound of Formula (L-IV)a can be produced by reaction in a similar manner to that in <Step 4> in (Production Method L).

<Step 6>

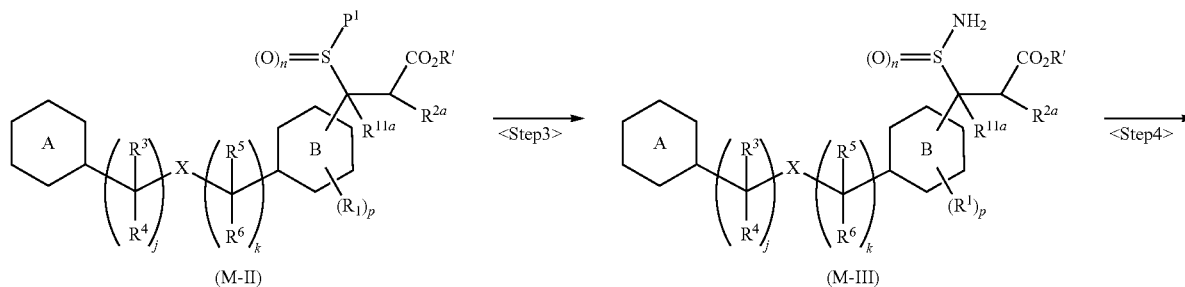
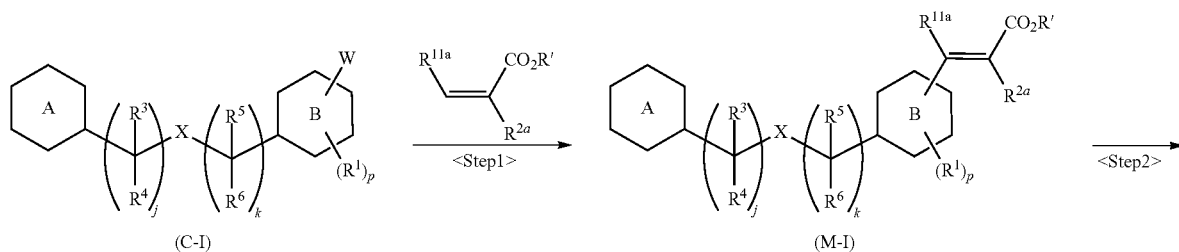
A compound of Formula (L-V)a can be produced by reac-
 30 tion in a similar manner to that in <Step 5> in (Production
 Method L).

<Step 7>

The compound of Formula (I)-1a/Formula (I)-2a can be
35 produced by reaction in a similar manner to that in <Step 6>
in (Production Method L).

<Production Method M>

(When W=halogen atom and n=2 in Formula)

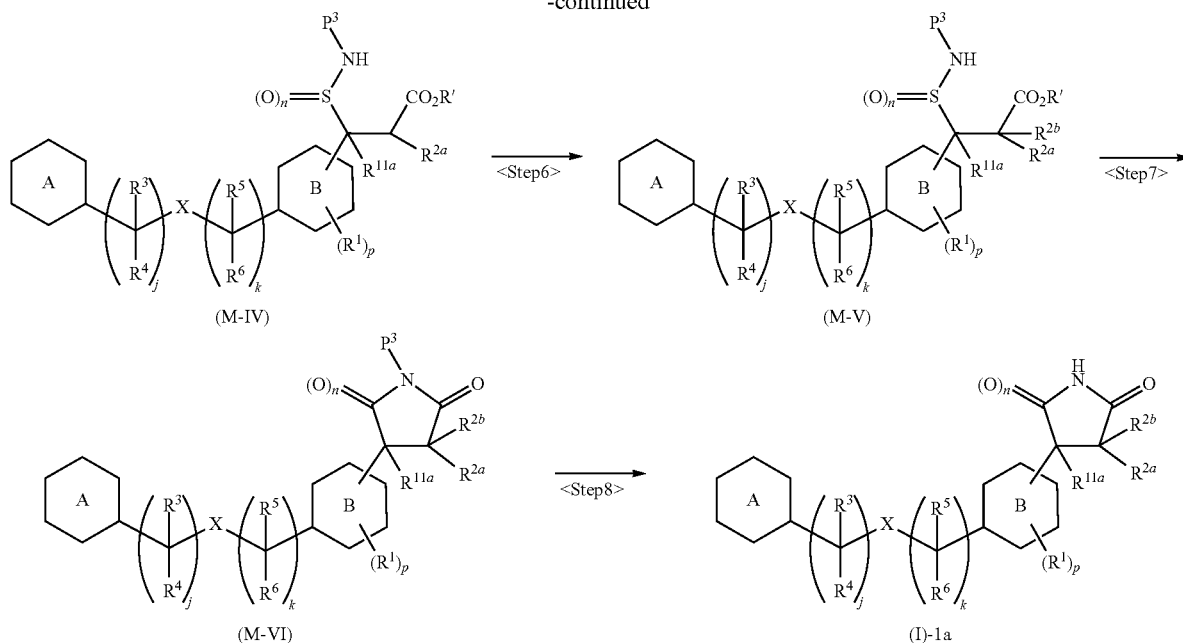


|<Step 5>

201

202

-continued



<Step 1>

A compound of Formula (C-I) is reacted. In accordance with methods known in literatures, for example, the method described in [Tetrahedron Letters, vol. 26 (22), pp. 2667-2670 (1985)], a compound of Formula (M-I) can be produced by reacting the compound of Formula (C-I) above in the presence of a palladium catalyst such as palladium diacetate, tetrakis triphenylphosphine palladium, and tris dibenzylideneacetone dipalladium and a base such as potassium carbonate, silver carbonate, and tributylamine using a reaction inert solvent such as acetonitrile, dioxane, tetrahydrofuran, benzene, toluene, dimethyl sulfoxide, and N,N-dimethylformamide or a mixed solvent of them at a temperature from room temperature to a reflux temperature of the solvent.

<Step 2>

The compound of Formula (M-I) is reacted. In accordance with methods known in literatures, for example, the method described in [Organic Letters, vol. 7 (22), pp. 5067-5069 (2005)], a compound of Formula (M-II) can be produced by reacting the compound of Formula (M-I) in the presence of a sulfur reagent such as sodium sulfite using a reaction inert solvent such as ethanol and water or a mixed solvent of them at a temperature from room temperature to a reflux temperature of the solvent or at high temperature and high pressure using a microwave reaction apparatus.

<Step 3>

The compound of Formula (M-II) is reacted. In accordance with methods known in literatures, for example, the method described in [Organic Letters, vol. 7 (22), pp. 5067-5069 (2005)], a compound of Formula (M-III) can be produced by reacting the compound of Formula (M-II) in the presence of a chlorinating reagent such as phosphorus pentachloride using a reaction inert solvent such as methylene chloride and DMF or a mixed solvent of them at a temperature from room temperature to a reflux temperature of the solvent and then by stopping the reaction with aqueous ammonia.

<Step 4>

The compound of Formula (M-III) is protected with a protective group P³. A compound of Formula (M-IV) can be

produced by causing the reaction of the compound of Formula (M-III) in a similar manner to that in <Step 2> in (Production Method B).

<Step 5>

The compound of Formula (M-II) is reacted. In accordance with methods known in literatures, for example, the method described in [Organic Letters, vol. 7 (22), pp. 5067-5069 (2005)], a compound of Formula (M-IV) can be produced by reacting the compound of Formula (M-II) in the presence of a chlorinating reagent such as phosphorus pentachloride using a reaction inert solvent such as methylene chloride and DMF or a mixed solvent of them at a temperature from room temperature to a reflux temperature of the solvent and then by stopping the reaction with a protected secondary amine such as benzylamine and tosylamine.

<Step 6>

<When R^{2b} ≠ hydrogen atom>

The compound of Formula (M-IV) is subjected to substitution reaction. In accordance with methods known in literatures, for example, the method described in [Jikken Kagaku Koza (Experimental Chemistry Course), the fifth edition, vol. 16, Synthesis of Organic Compound IV, Carboxylic acid, Amino acid, and Peptide, pp. 1-70 (2005), Maruzen Co., Ltd.], a compound of Formula (M-V) can be produced by reacting the compound of Formula (M-IV) with, for example, a halogenated alkyl of R^{2b}X in the presence of a base such as sodium ethoxide, sodium methoxide, sodium hydride, lithium hydride, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, and potassium carbonate using a reaction inert solvent such as ethanol, water, N,N-dimethylformamide, 1,4-dioxane, and tetrahydrofuran or a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 7>

The compound of Formula (M-V) is subjected to ring formation reaction. In accordance with methods known in literatures, for example, the method described in [Organic Letters, vol. 7 (22), pp. 5067-5069 (2005)], a compound of Formula (M-VI) can be produced by reacting the compound of Formula (M-V) in the presence of sodium methoxide,

203

sodium ethoxide, or the like using a reaction inert solvent such as methanol and ethanol or a mixed solvent of them at a temperature from room temperature to a reflux temperature of the solvent.

<Step 8>

The protective group P^3 in the compound of Formula (M-VI) is deprotected. The compound of Formula (I)-1a can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

(7) The methods for producing the compound of Formula (I)-1b of the present invention will be described below.

<Production Method N>

(When $n=2$ in Formula)

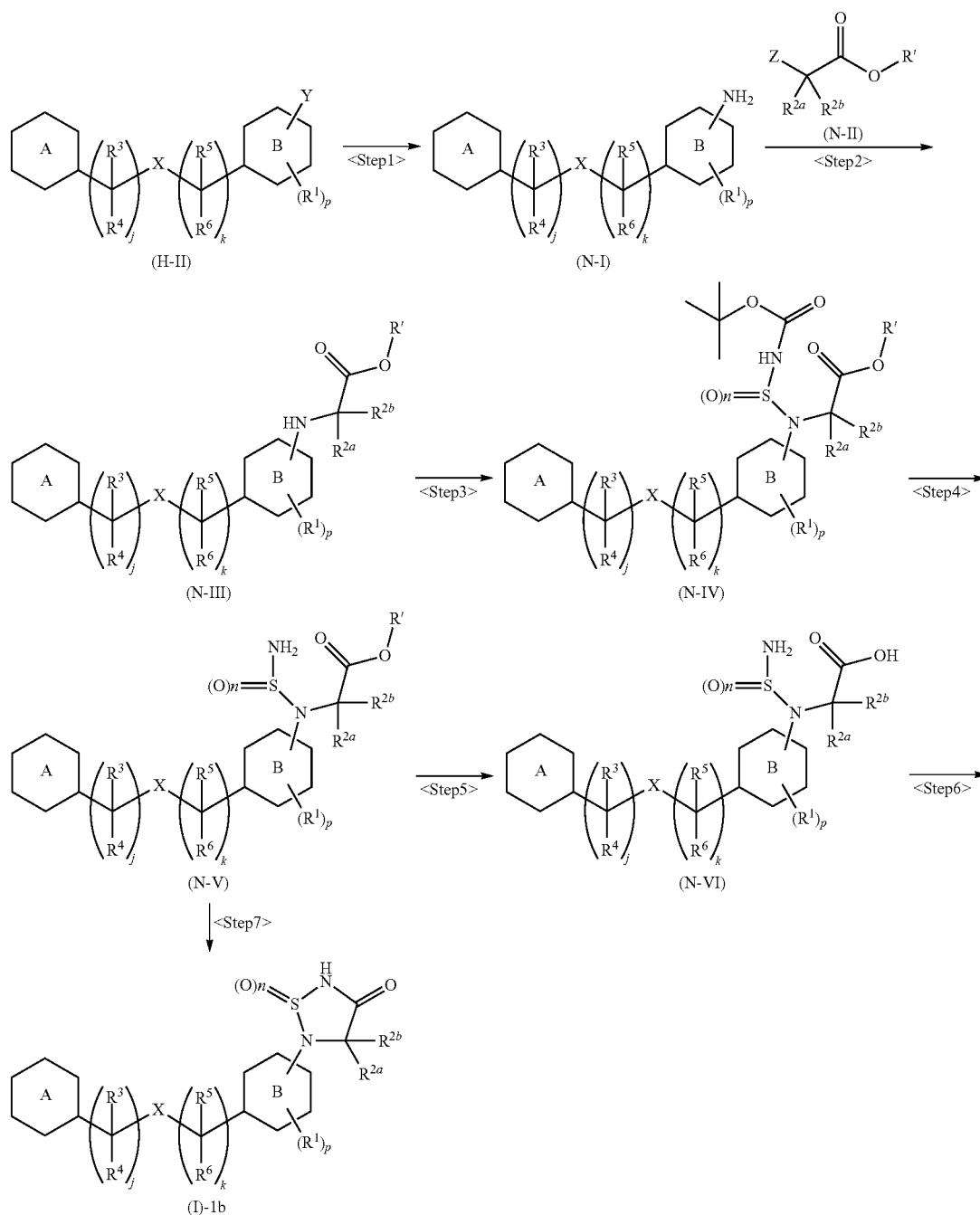
204

<Step 1>

A compound of Formula (N-I) can be produced by reacting the compound of Formula (H-II) above ($Y=\text{protected imino group } (-\text{NP}^1_2)$) in a similar manner to that in <Step 3> in (Production Method B).

<Step 2>

The compound of Formula (N-I) is reacted. In accordance with methods known in literatures, for example, the method described in [Chemical & Pharmaceutical Bulletin, vol. 43 (5), pp. 820-841 (1995)], a compound of Formula (N-III) can be produced by substitution reaction of the compound of Formula (N-I) in the presence of a compound of Formula (N-II), which is known in the art or can be easily produced



205

from a known compound, in the presence or absence of a base such as diisopropylethylamine, triethylamine, pyridine, sodium hydride, sodium hydroxide, potassium carbonate, and cesium carbonate in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 3>

The compound of Formula (N-III) is reacted. In accordance with methods known in literatures, for example, the method described in [WO 2007/110337 pamphlet], each compound of Formula (N-IV) (n=0, 1, or 2) can be produced by reacting the compound of Formula (N-III), for example, in the presence of a sulfur reagent such as carbamic acid n-(chlorosulfonyl)-1,1-dimethylethyl ester and in the presence or absence of a base such as diisopropylethylamine, triethylamine, pyridine, sodium hydride, sodium hydroxide, potassium carbonate, and cesium carbonate in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

<Step 4>

The compound of Formula (N-IV) is deprotected. A compound of Formula (N-V) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 5>

The compound of Formula (N-V) is hydrolyzed. A compound of Formula (N-VI) can be produced by reaction in a similar manner to that in <Step 2> in (Production Method E).

<Step 6>

The compound of Formula (N-VI) is subjected to ring formation reaction. The compound of Formula (I)-1b can be produced by reaction in a similar manner to that in <Step 3> in (Production Method E) (in the absence of ammonia).

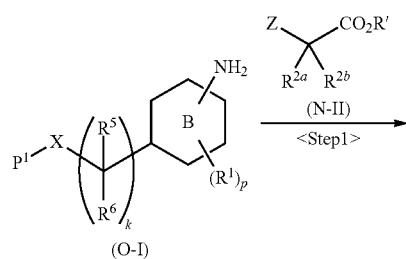
<Step 7>

The compound of Formula (N-V) is subjected to ring formation reaction. The compound of Formula (I)-1b can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

The compounds of Formula (II)-1b and Formula (III)-1b above are included in the compound of Formula (I)-1b in (Production Method N) and can be produced by a similar production method, and these compounds of Formula (I)-1b are included in the compound of Formula (I).

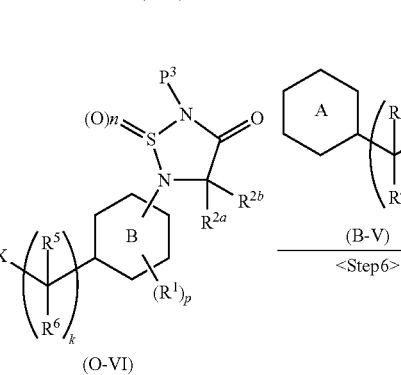
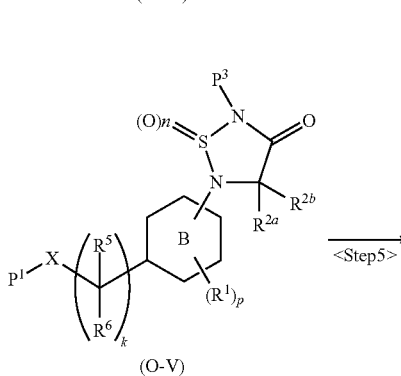
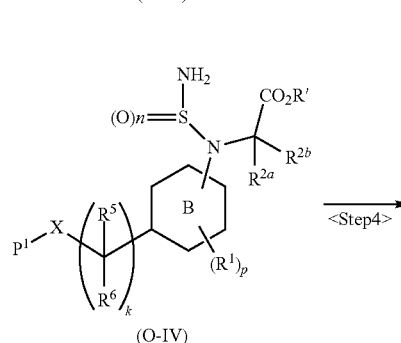
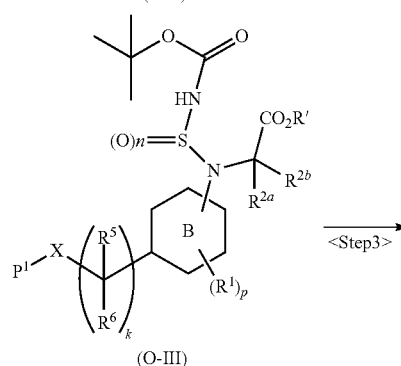
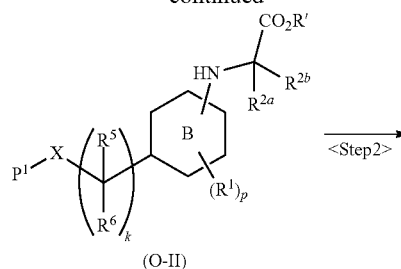
<Production Method O>

(When n=2 in Formula)



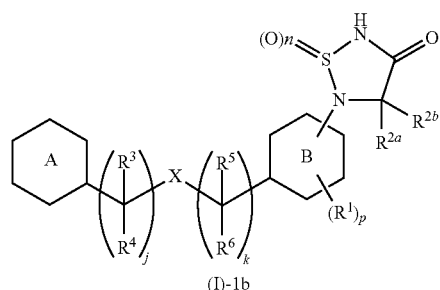
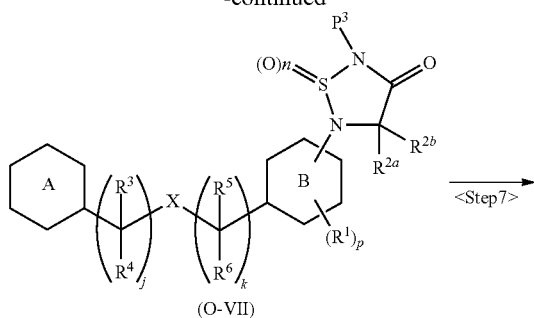
206

-continued



207

-continued



<Step 1>

A compound of Formula (O-I) is reacted. A compound of Formula (O-II) can be produced by reacting the compound of Formula (O-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (N-II) in a similar manner to that in <Step 2> in (Production Method N).

208

<Step 2>

The compound of Formula (O-II) is reacted. A compound of Formula (O-III) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method N).

<Step 3>

The compound of Formula (O-III) is deprotected. A compound of Formula (O-VI) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 4>

The compound of Formula (O-VI) is subjected to ring formation reaction.

A compound of Formula (O-V) can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

<Step 5>

The protective group P¹ in the compound of Formula (O-V) is deprotected. A compound of Formula (O-VI) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 6>

The compound of Formula (O-VI) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (O-VII) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

<Step 7>

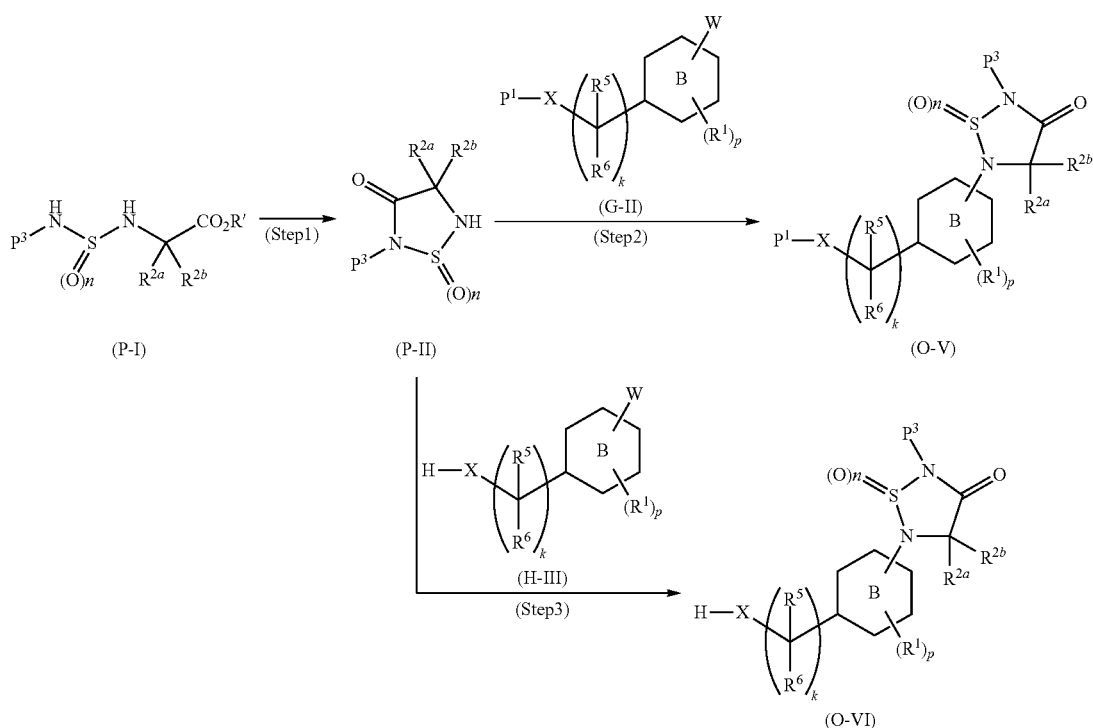
The protective group P³ in the compound of Formula (O-VII) is deprotected. The compound of Formula (I-1b) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

The compounds of Formula (II)-1b and Formula (III)-1b above are included in the compound of Formula (I)-1b in (Production Method O) and can be produced by a similar production method, and these compounds of Formula (I)-1b are included in the compound of Formula (I).

(7-1) The compounds of Formula (O-V) and Formula (O-VI) can also be produced by the method below.

<Production Method P>

(When n=2 in Formula)



209

<Step 1>

A compound of Formula (P-I) is subjected to ring formation reaction. A compound of Formula (P-II) can be produced by reacting the compound of Formula (P-I) that can be produced in accordance with methods known in literatures, for example, the method described in [Bioorganic & Medicinal Chemistry, vol. 16 (7), pp. 3550-3556 (2008)] in a similar manner to that in <Step 7> in (Production Method M).

<Step 2>

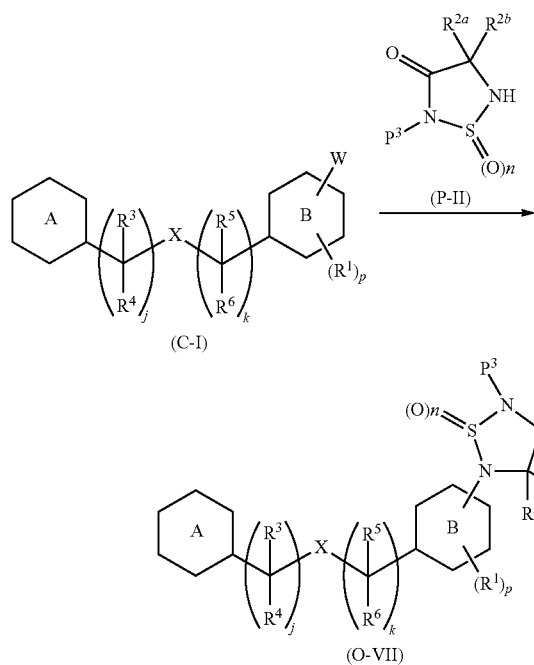
The compound of Formula (P-II) is subjected to substitution reaction with a compound of Formula (G-II). [When W=halogen in Formula] The compound of Formula (O-V) can be produced by using the compound of Formula (P-II) and the compound of Formula (G-II) above in accordance with methods known in literatures, for example, the method described in [WO 2007/067615 pamphlet]. [When W=boronic acid or boronic ester in Formula] The compound of Formula (O-V) can be produced by using the compound of Formula (P-II) and the compound of Formula (G-II) above in accordance with methods known in literatures, for example, the method described in [Bioorganic & Medicinal Chemistry, vol. 14 (17), pp. 5833-5849 (2006)].

<Step 3>

The compound of Formula (P-II) is subjected to substitution reaction with a compound of Formula (H-III). The compound of Formula (O-VI) can be produced by causing the compound of Formula (P-II) to react with the compound of Formula (H-III) above in a similar manner to that in <Step 2> in (Production Method P).

(7-2) The compound of Formula (O-VII) can also be produced by the method below.

<Production Method Q>



A compound of Formula (C-I) that is easily obtained from a known compound by the method in (Production Method H) is subjected to substitution reaction with a compound of Formula (P-II). The compound of Formula (O-VII) can be produced by reaction in a similar manner to that in <Step 2> in (Production Method P).

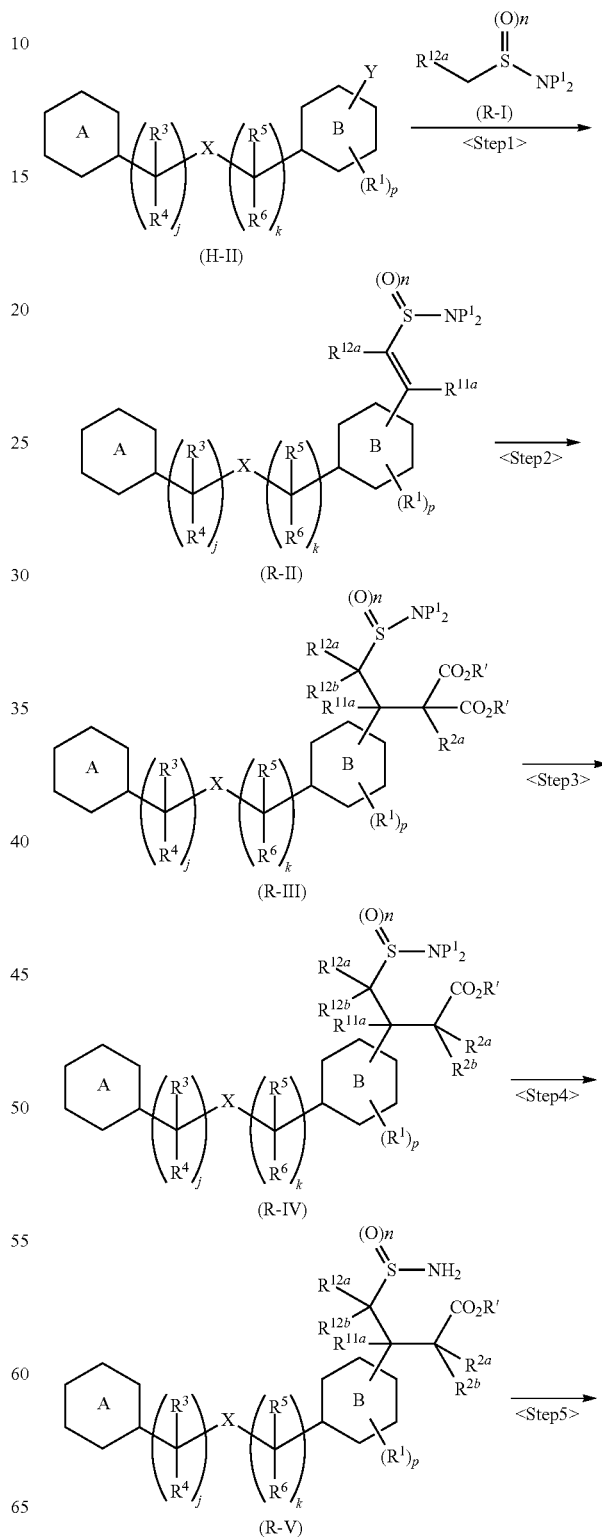
210

(8) The method for producing the compound of Formula (I)-1c of the present invention will be described below.

<Production Method R>

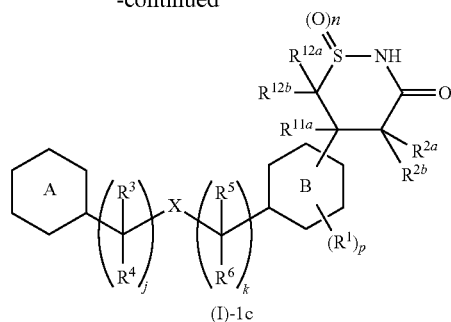
<When $R^{2a}=R^{2b}=H$, $R^{12b}=H$, alkyl, alkenyl, or alkynyl in Formula (I)-c above>

(In Formula, $n=2$ and Y =formyl group or COR^{11a} group)



211

-continued



<Step 1>

A compound of Formula (H-II) is reacted with a compound of Formula (R-I). In accordance with methods known in literatures, for example, the method described in [Synlett, vol. 5, pp. 843-838 (2005)], a compound of Formula (R-II) can be produced by reacting the compound of Formula (H-II) that is easily obtained from a known compound by the method in <Step 1> in (Production Method H) with the compound of Formula (R-I) in the presence of a base such as hexamethyldisilazane lithium and potassium tert-butoxide, diethyl chlorophosphate, and the like in a reaction inert solvent including an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from -78°C . to a reflux temperature of the solvent.

<Step 2>

The compound of Formula (R-II) is reacted. In accordance with methods known in literatures, for example, the method described in [Heterocyclic Communications, vol. 3 (1), pp. 19-22 (1995)], a compound of Formula (R-III) can be produced by reacting the compound of Formula (R-II) in the presence of a malonic acid ester and a base such as sodium hydride, potassium tert-butoxide, sodium methoxide, and sodium methoxide in a reaction inert solvent including an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

<Step 3>

The compound of Formula (R-III) is reacted. In accordance with methods known in literatures, for example, the method described in [Chemical & Pharmaceutical Bulletin, vol. 33 (12), pp. 5316-5327 (1985)], a compound of Formula (R-IV) can be produced by substitution reaction in the presence of the compound of Formula (R-III) in the presence or absence of sodium chloride in a reaction inert solvent including a polar solvent such as dimethyl sulfoxide and N,N-dimethylformamide or in a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

<Step 4>

The protective group P^1 in the compound of Formula (R-IV) is deprotected. A compound of Formula (R-V) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 5>

The compound of Formula (R-V) is subjected to ring formation reaction. The compound of Formula (I)-1c can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

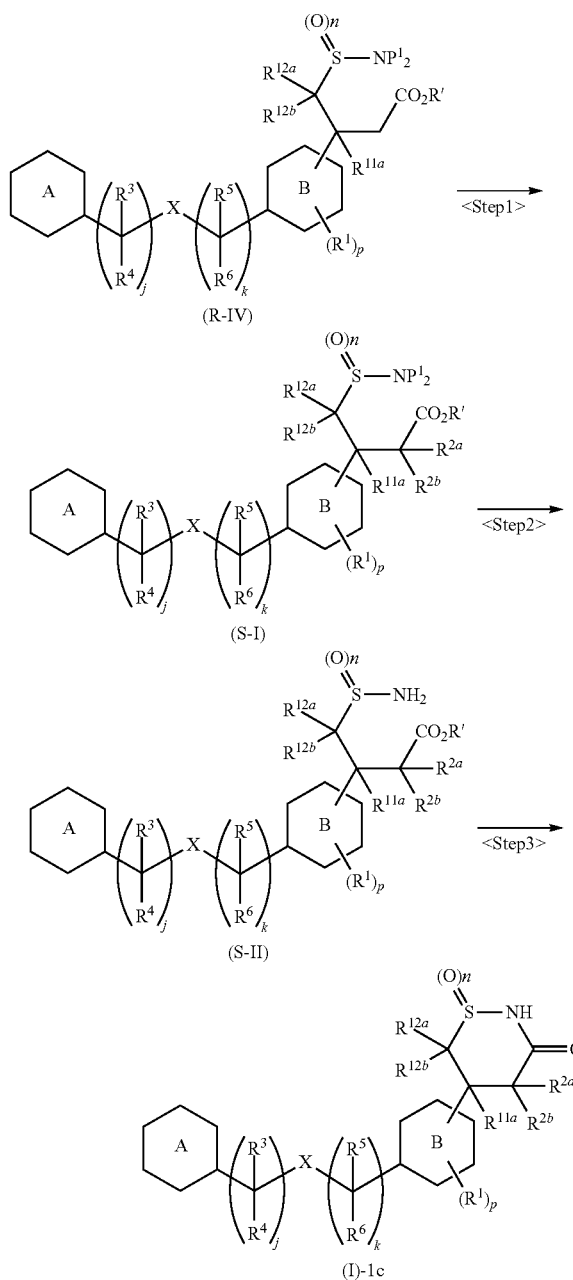
212

The compounds of Formula (II)-1c and Formula (III)-1c above are included in the compound of Formula (I)-1c in (Production Method R) and can be produced by a similar production method, and these compounds of Formula (I)-1c are included in the compound of Formula (I). Similarly, in the production methods in (Production Method S) or later, the compounds of Formula (II)-1c and Formula (III)-1c are included in the compound of Formula (I)-1c and can be produced by a similar production method, and these compounds of Formula (I)-1c are included in the compound of Formula (I).

<Production Method S>

<When R^{2a} and/or $\text{R}^{2b} \neq \text{H}$ and $\text{R}^{12b} = \text{H}$ in Formula (I)-1c above>

(When $n=2$ in Formula)



213

<Step 1>

A compound of Formula (R-IV) is subjected to substitution reaction. A compound of Formula (S-I) can be produced by reaction in a similar manner to that in <Step 6> in (Production Method M).

<Step 2>

The protective group P^1 in the compound of Formula (S-I) is deprotected. A compound of Formula (S-II) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

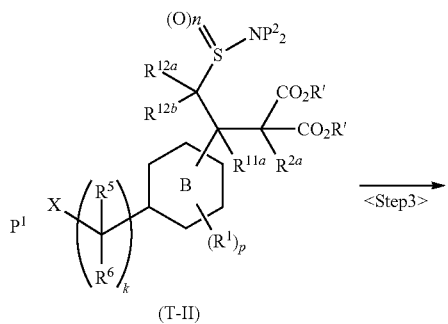
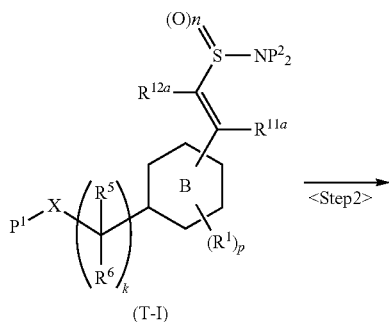
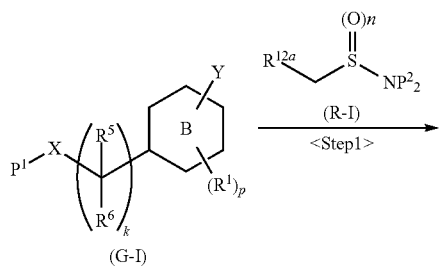
<Step 3>

The compound of Formula (S-II) is subjected to ring formation reaction. The compound of Formula (I)-1c can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

<Production Method T>

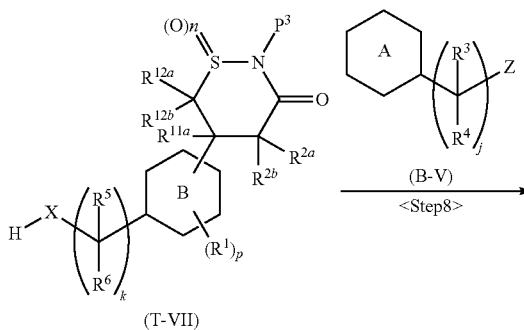
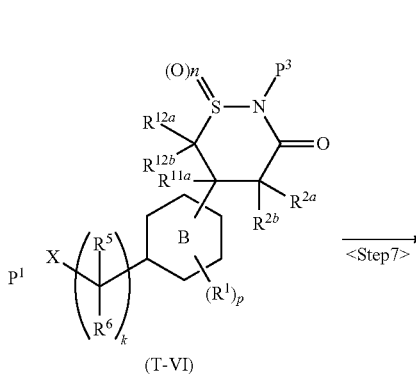
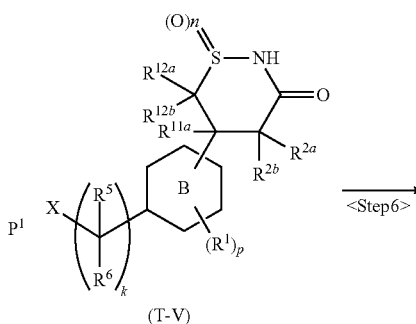
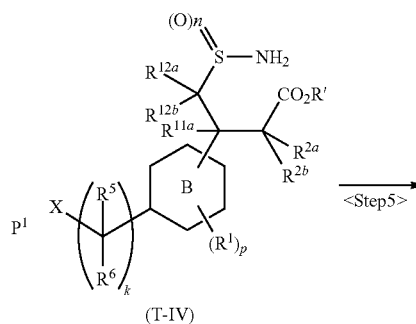
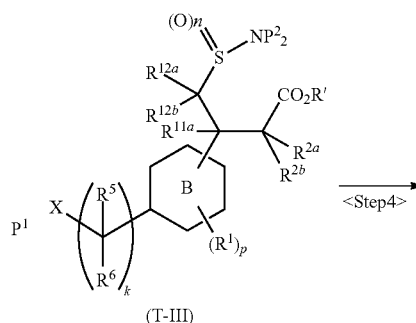
<When R^{12b} =H, alkyl, alkenyl, or alkynyl in Formula (I)-1c above>

(In Formula, $n=2$ and Y =formyl group or COR^{11a} group)



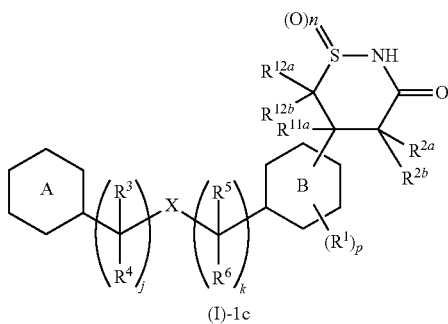
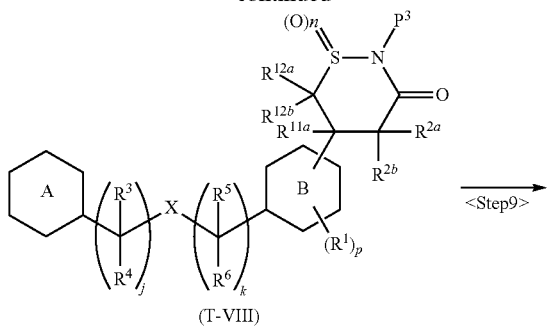
214

-continued



215

-continued



<Step 1>

A compound of Formula (G-I) is reacted. A compound of Formula (T-I) can be produced by reacting a compound of Formula (G-I), which is known in the art or can be easily produced from a known compound, with a compound of Formula (R-I) in a similar manner to that in <Step 1> in (Production Method R).

<Step 2>

The compound of Formula (T-I) is reacted. A compound of Formula (T-II) can be produced by reaction in a similar manner to that in <Step 2> in (Production Method R).

216

<Step 3>

The compound of Formula (T-II) is reacted. A compound of Formula (T-III) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method R).

5 <Step 4>

The protective group P² in the compound of Formula (T-III) is deprotected. A compound of Formula (T-IV) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

10 <Step 5>

The compound of Formula (T-IV) is subjected to ring formation reaction. A compound of Formula (T-V) can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

<Step 6>

The compound of Formula (T-V) is protected with a protective group P³. A compound of Formula (T-VI) can be produced by causing the reaction of the compound of Formula (T-V) in a similar manner to that in <Step 2> in (Production Method B).

20 <Step 7>

The protective group P¹ in the compound of Formula (T-VI) is deprotected. A compound of Formula (T-VII) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

25 <Step 8>

The compound of Formula (T-VII) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (T-VIII) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

<Step 9>

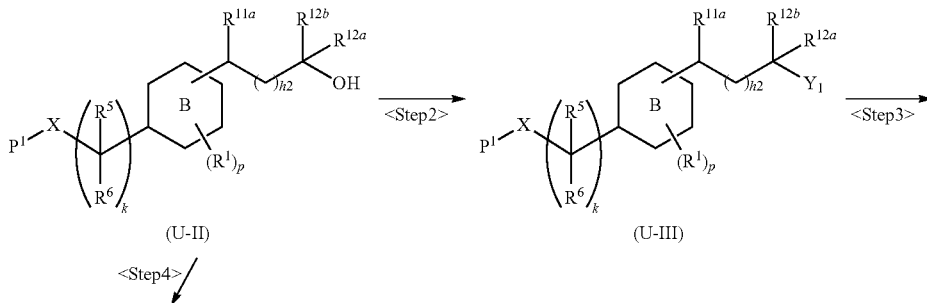
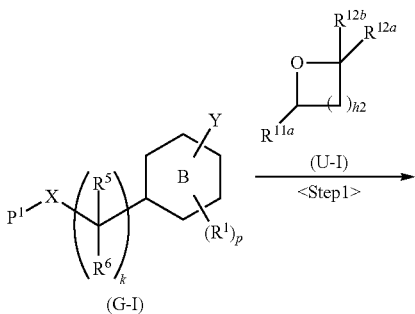
The protective group P³ in the compound of Formula (T-VIII) is deprotected. The compound of Formula (I)-1c can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

(8-1) The compound of Formula (I)-1c or Formula (I)-1f
35 can also be produced by the method below.

<Production Method U>

<When $J_1=J_{1a}=CR^{11a}$, $J_2=CR^{12a}R^{12b}$, and $h=1$ to 3 in Formula (I) above, that is, in the case of Formula (I)-1c or Formula (I)-1f>

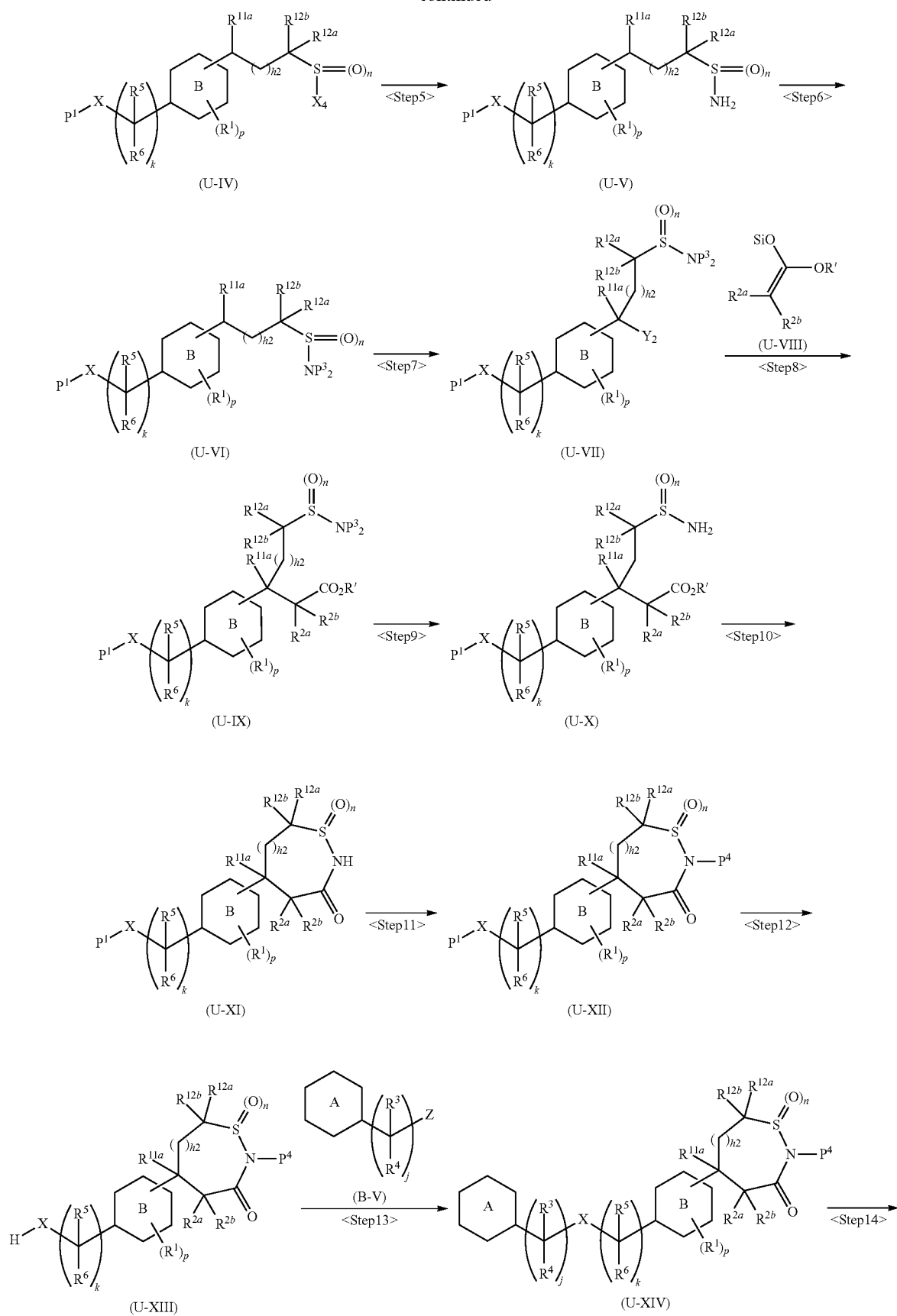
(In Formula, n=2 and Y=halogen)



217

218

-continued



(I)-1c/(I)-1f

The compound of Formula (U-VI) is subjected to substitution reaction with a carboxylic acid methyl ester. In accordance with, for example, the method described in [Tetrahedron, vol. 65 (28), pp. 5462-5471 (2009)], a compound of

221

Formula (U-VIII) can be produced by using the compound of Formula (U-VI), indium bromide (InBr_3), and a silyl enolate of Formula (U-VIII).

<Step 9>

The protective group P^3 in the compound of Formula (U-IX) is deprotected. A compound of Formula (U-X) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 10>

The compound of Formula (U-X) is subjected to ring formation reaction. A compound of Formula (U-XI) can be produced by reaction in a similar manner to that in <Step 7> in (Production Method M).

<Step 11>

The compound of Formula (U-XI) is protected with a protective group P^4 . A compound of Formula (U-XII) can be produced by causing the reaction of the compound of Formula (U-XI) in a similar manner to that in <Step 2> in (Production Method B).

<Step 12>

The protective group P^1 in the compound of Formula (U-XII) is deprotected. A compound of Formula (U-XIII) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 13>

The compound of Formula (U-XIII) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (U-XIV) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

<Step 14>

The protective group P^4 in the compound of Formula (U-XIV) is deprotected. The compound of Formula (I)-1c (when $\text{h}_2=0$) or Formula (I)-1f (when $\text{h}_2=1$ or 2) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

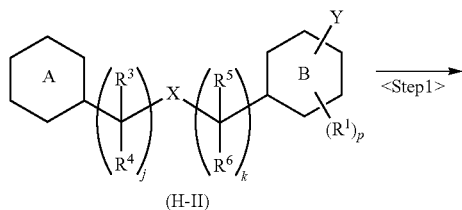
The compounds of Formula (II)-1f and Formula (III)-1f above are included in the compound of Formula (I)-1f in (Production Method U) and can be produced by a similar production method, and these compounds of Formula (I)-1f are included in the compound of Formula (I).

In Formula (I) above, Formula (I)-1c and Formula (I)-1f include optical isomers. The isomers can be separated through optical resolution using chiral column chromatography or asymmetric synthesis by a person skilled in the art based on conventional techniques.

(9) The methods for producing the compound of Formula (I)-1d of the present invention will be described below.

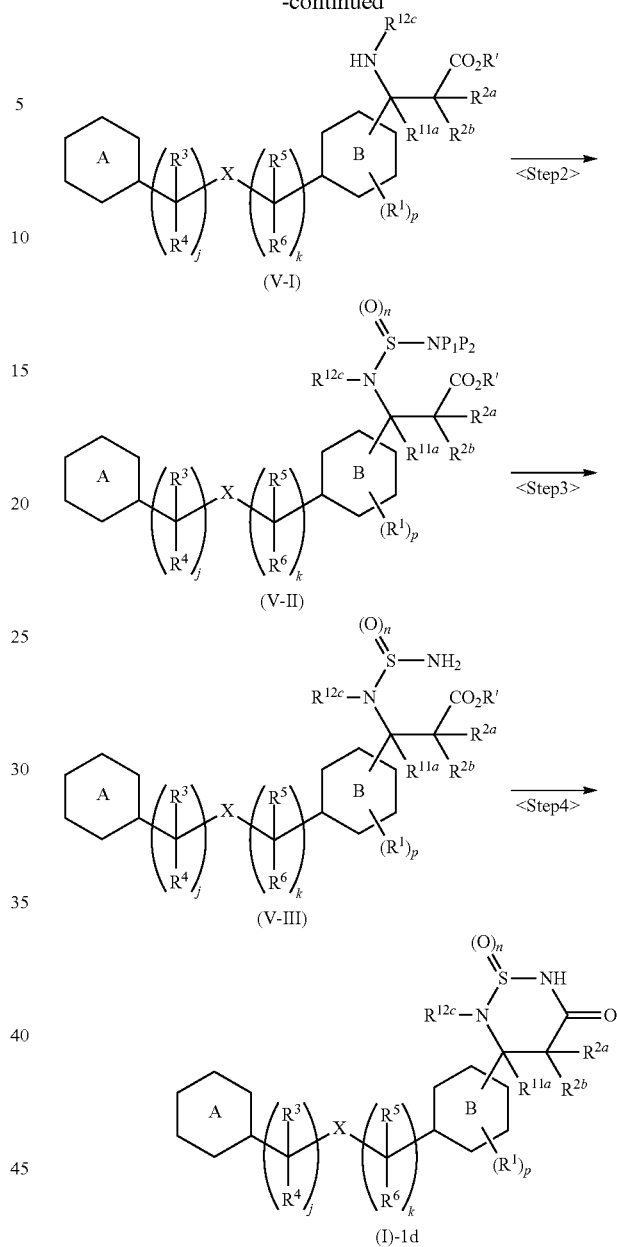
<Production Method V>

<When $n=1$ to 2, $\text{R}^{2a}=\text{R}^{2b}=\text{H}$, $\text{Y}=\text{CH}=\text{CH}-\text{COOR}'$, and $n=2$ in Formula (I)-1d above>



222

-continued



<Step 1>

A compound of Formula (H-II) is reacted. In accordance with methods known in literatures, for example, the method described in [Journal of Organic Chemistry, vol. 50 (13), pp. 2259-2263 (1985)], a compound of Formula (V-I) can be produced by reacting the compound of Formula (H-II) that is easily obtained from a known compound by the method in <Step 1> in (Production Method H) in the presence of an amine such as ammonium acetate, an alkyl ammonium, and aqueous ammonia, malonic acid, and the like in a reaction inert solvent including a polar solvent such as ethanol, butanol, and water or in a mixed solvent of them at a temperature from 0°C . to a reflux temperature of the solvent.

<Step 2>

The compound of Formula (V-I) is reacted. In accordance with methods known in literatures, for example, the method described in [Synlett, vol. 5, pp. 843-838 (2005)], a com-

223

compound of Formula (V-II) can be produced by reacting the compound of Formula (V-I) with a sulfur agent such as an N-chlorosulfonylcarbamic acid ester in the presence of a base such as sodium hydride, sodium hydroxide, triethylamine, and pyridine in a reaction inert solvent including an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as methanol, ethanol, and N,N-dimethylformamide or in a mixed solvent of them at a temperature from -78°C . to a reflux temperature of the solvent.

<Step 3>

The protective groups P^1 and P^2 in the compound of Formula (V-II) are deprotected. A compound of Formula (V-III) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 4>

The compound of Formula (V-V) is subjected to ring formation reaction. The compound of Formula (I)-1d can be produced by reaction in a similar manner to that in

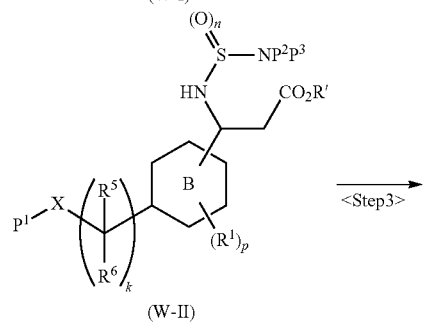
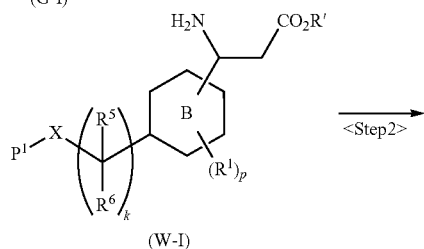
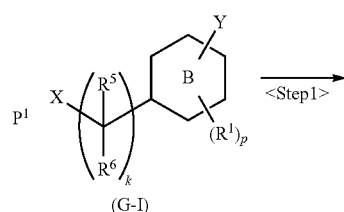
<Step 7> in (Production Method M).

The compounds of Formula (II)-1d and Formula (III)-1d above are included in the compound of Formula (I)-1d in (Production Method V) and can be produced by a similar production method, and these compounds of Formula (I)-1d are included in the compound of Formula (I).

Similarly, in the production methods in (Production Method W) or later, the compounds of Formula (II)-1d and Formula (III)-1d above are included in the compound of Formula (I)-1d and can be produced by a similar production method, and these compounds of Formula (I)-1d are included in the compound of Formula (I).

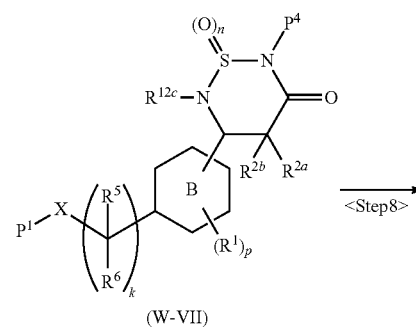
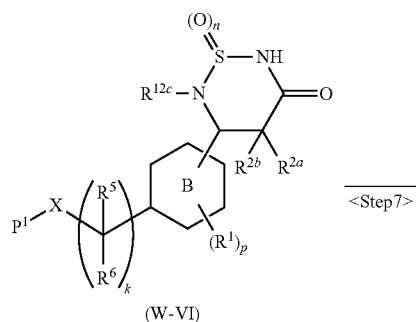
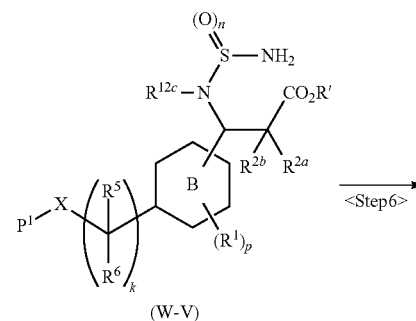
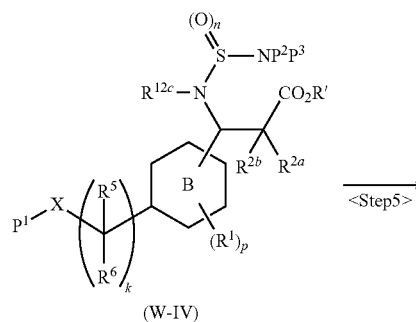
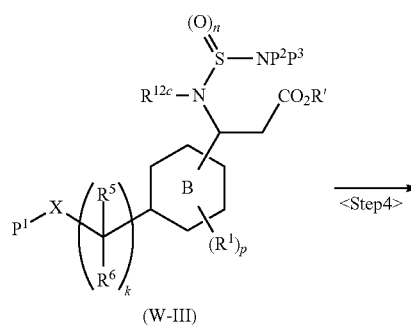
<Production Method W>

<When $n=2$ and $R^{11a}=H$ >

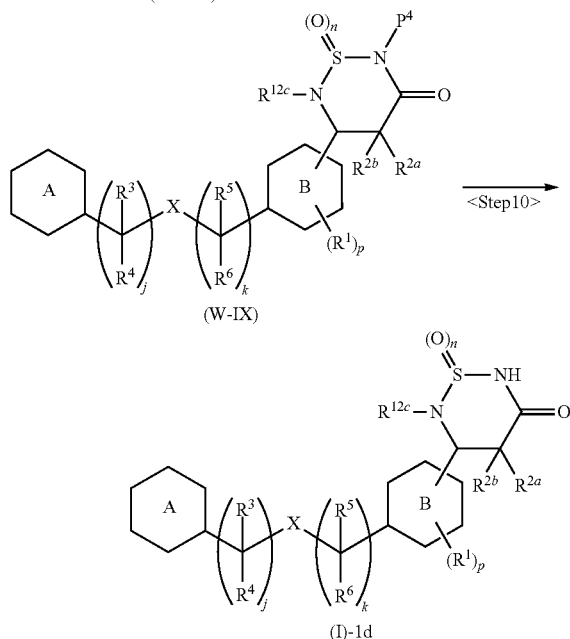
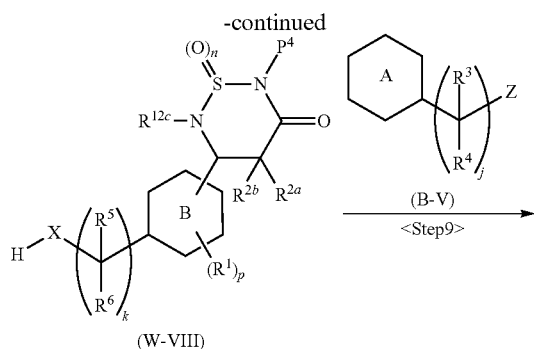


224

-continued



225



<Step 1>

A compound of Formula (G-I) is reacted. A compound of Formula (W-I) can be produced by reacting the compound of Formula (G-I), which is known in the art or can be easily produced from a known compound, in a similar manner to that in <Step 1> in

(Production Method V).

<Step 2>

The compound of Formula (W-I) is reacted. A compound of Formula (W-II) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method V).

<Step 3>

<When $R^{12c} \neq$ hydrogen atom>

The compound of Formula (W-II) is reacted. In accordance with methods known in literatures, for example, the method described in [Synlett, vol. 5, pp. 697-699 (2002)], a compound of Formula (W-III) can be produced by reacting the compound of Formula (W-II) with a compound of $R^{12c}OH$ in the presence of an organophosphorus compound such as triphenylphosphine and an azo compound such as an azodicarboxylic acid ester and azodicarboxylic amide in a reaction inert solvent including a halogenated solvent such as dichloromethane and chloroform, an ether solvent such as diethyl ether and tetrahydrofuran, an aromatic hydrocarbon solvent such as toluene and benzene, and a polar solvent such as N,N-dimethylformamide and dimethyl sulfoxide or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

226

<Step 4>

<When R^{2a} and/or $R^{2b} \neq$ hydrogen atom>

The compound of Formula (W-III) is subjected to substitution reaction. A compound of Formula (W-IV) can be produced by reaction in a similar manner to that in <Step 6> in (Production Method M).

<Step 5>

The protective groups P^2 and P^3 in the compound of Formula (W-IV) are deprotected. A compound of Formula (W-V) can be produced by causing the reaction of the compound of Formula (W-IV) in a similar manner to that in <Step 3> in (Production Method B).

<Step 6>

The compound of Formula (W-V) is subjected to ring formation reaction. A compound of Formula (W-VI) can be produced by causing the reaction of the compound of Formula (W-V) in a similar manner to that in <Step 7> in (Production Method M).

<Step 7>

The compound of Formula (W-VI) is protected with a protective group P^4 . A compound of Formula (W-VII) can be produced by causing the reaction of the compound of Formula (W-VI) in a similar manner to that in <Step 2> in (Production Method B).

<Step 8>

The protective group P^1 in the compound of Formula (W-VII) is deprotected. A compound of Formula (W-VIII) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 9>

The compound of Formula (W-VIII) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (W-IX) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

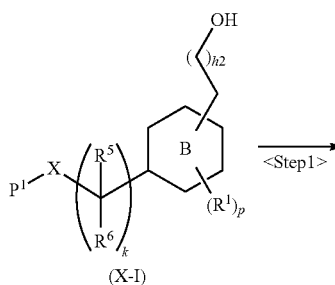
<Step 10>

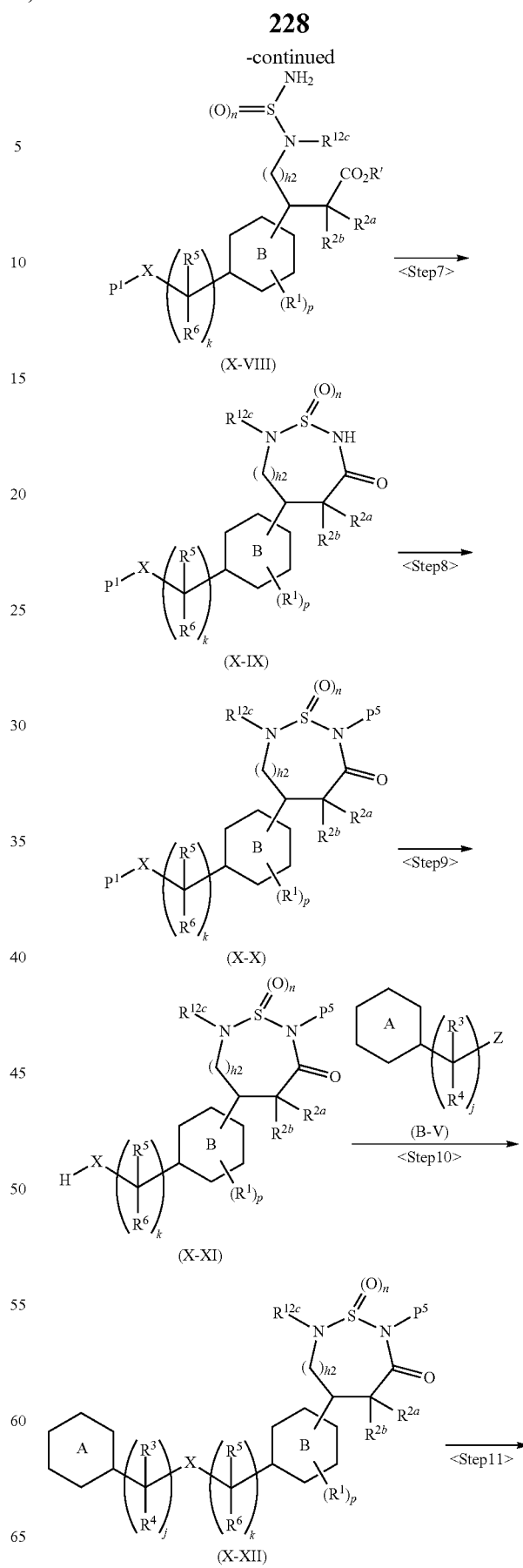
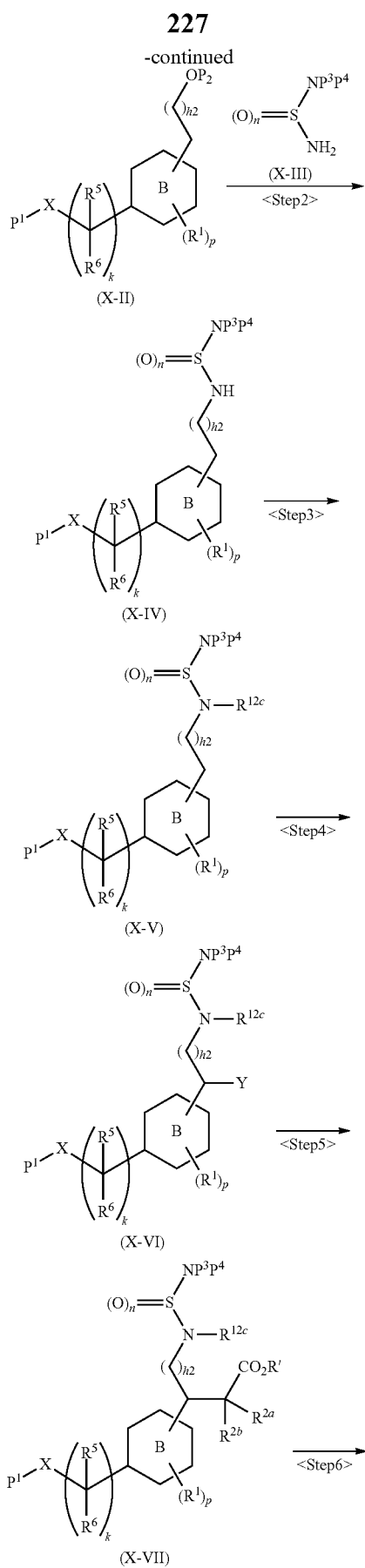
The protective group P^4 in the compound of Formula (W-IX) is deprotected. The compound of Formula (I-1d) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

(9-1) The compound of Formula (I-1d or Formula (I-1e) can also be produced by the method below.

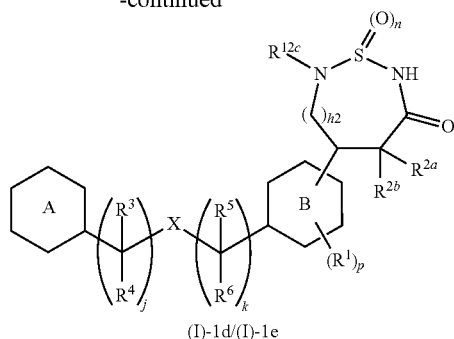
<Production Method X>

<When $J_1=J_{1a}=CR^{11a}$, $J_2=NR^{12c}$, and $h=1$ to 3 in Formula (I) above, that is, in the case of Formula (I-1d or Formula (I-1e) and when $n=2$ and $R^{11a}=H$ >





-continued



<Step 1>

A compound of Formula (X-I) is protected with a protective group P². A compound of Formula (X-II) can be produced by reacting the compound of Formula (X-I) that is obtained in (Production Method Y) or (Production Method Z) described later in a similar manner to that in <Step 2> in (Production Method B).

<Step 2>

The compound of Formula (X-II) is reacted. A compound of Formula (X-IV) can be produced from the compound of Formula (X-II) and a compound of Formula (X-III) in accordance with, for example, the method described in [Synlett, vol. 6, pp. 833-836 (2006)].

<Step 3>

<When $R^{12c} \neq$ hydrogen atom>

The compound of Formula (X-IV) is reacted. A compound of Formula (X-V) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method W).

<Step 4>

The compound of Formula (X-V) is subjected to substitution reaction. A compound of Formula (X-VI) can be produced by reaction in a similar manner to that in <Step 2> in (Production Method U).

<Step 5>

The compound of Formula (X-VI) is subjected to substitution reaction. A compound of Formula (X-VII) can be produced from the compound of Formula (X-VI) in accordance with, for example, the method described in [Journal of the American Chemical Society, vol. 73, pp. 3987-3993 (1953)].

<Step 6>

The protective groups P³ and P⁴ in the compound of Formula (X-VII) are deprotected. A compound of Formula (X-VIII) can be produced by causing the reaction of the compound of Formula (X-VII) in a similar manner to that in <Step 3> in (Production Method B).

<Step 7>

The compound of Formula (X-VIII) is subjected to ring formation reaction. A compound of Formula (X-IX) can be produced by causing the reaction of the compound of Formula (X-VIII) in a similar manner to that in <Step 7> in (Production Method M).

<Step 8>

The compound of Formula (X-IX) is protected with a protective group P⁵. A compound of Formula (X-X) can be produced by causing the reaction of the compound of Formula (X-IX) in a similar manner to that in <Step 2> in (Production Method B).

<Step 9>

The protective group P¹ in the compound of Formula (X-X) is deprotected. A compound of Formula (X-XI) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

<Step 10>

The compound of Formula (X-XI) is subjected to substitution reaction with a compound of Formula (B-V). A compound of Formula (X-XII) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

<Step 11>

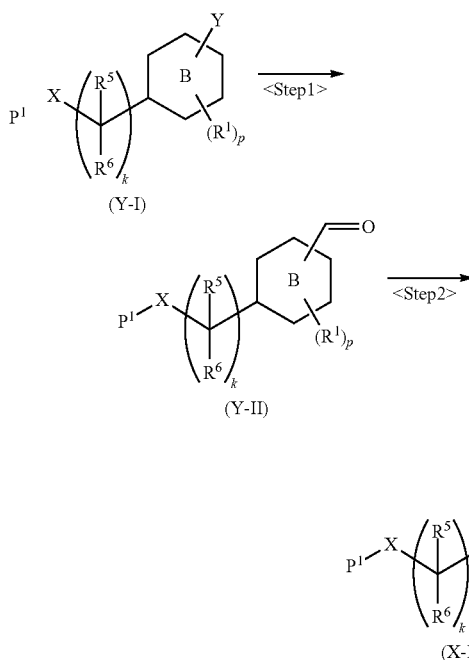
The protective group P⁵ in the compound of Formula (X-XII) is deprotected. The compound of Formula (I)-1d (when h₂=0) or Formula (I)-1e (when h₂=1 or 2) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

The compounds of Formula (II)-1e and Formula (III)-1e above are included in the compound of Formula (I)-1e in (Production Method X) and can be produced by a similar production method, and these compounds of Formula (I)-1e are included in the compound of Formula (I).

(9-2) Next, methods for producing the compound of Formula (X-I) will be described.

<Production Method Y>

<When h2=0 and Y=halogen atom in Formula (X-I) above>



<Step 1>

A compound of Formula (Y-I) is reacted. In accordance with methods known in literatures, for example, the method described in [Tetrahedron, vol. 57 (24), pp. 5243-5253 (2001)], a compound of Formula (Y-II) can be produced by reacting the compound of Formula (Y-I) in the presence of a base such as n-butyllithium and dimethylformamide in a reaction inert solvent including an ether solvent such as diethyl ether and tetrahydrofuran and an aromatic hydrocarbon solvent such as hexane, toluene, and benzene or in a mixed solvent of them at a temperature from 0° C. to a reflux temperature of the solvent.

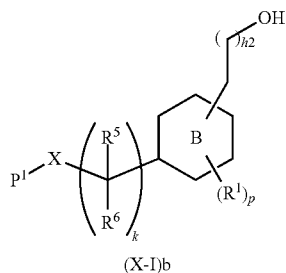
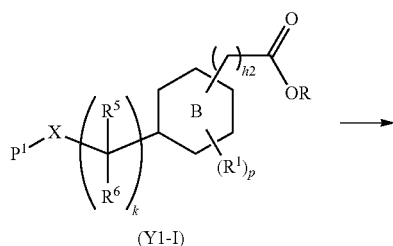
<Step 2>

The compound of Formula (Y-II) is subjected to reduction. The compound of Formula (X-I)a can be produced by reacting the compound of Formula (Y-II) in a similar manner to that in <Step 2> in (Production Method J-1).

231

<Production Method Y-1>

<When h2=1 to 2 in Formula (X-I) above>

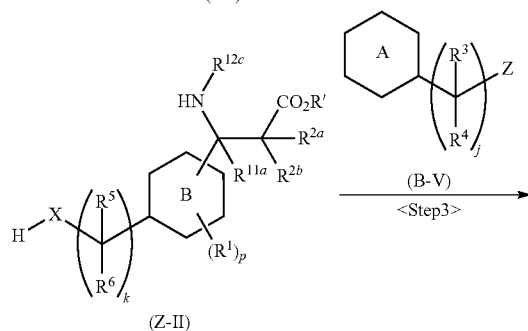
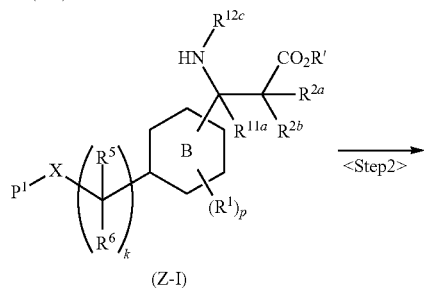
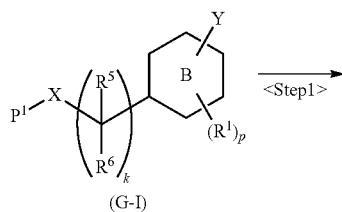


A compound of Formula (Y1-I) is subjected to reduction. The compound of Formula (X-I)b can be produced by reacting the compound of Formula (Y1-I) in a similar manner to that in <Step 2> in (Production Method J-1).

(9-3) The compound of Formula (V-II) can also be produced by the method below.

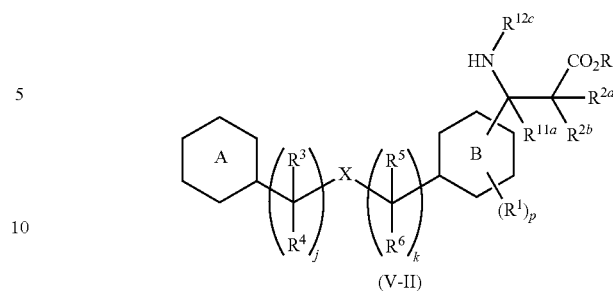
<Production Method Z>

<Y=—CH=CH—COOR' in Formula>



232

-continued



<Step 1>

A compound of Formula (Z-I) can be produced by using a compound of Formula (G-I), which is known in the art or can be easily produced from a known compound, by the method in <Step 1> and <Step 2> or <Step 3> in (Production Method V).

<Step 2>

The protective group P¹ in the compound of Formula (Z-I) is deprotected. A compound of Formula (Z-II) can be produced by reaction in a similar manner to that in <Step 3> in (Production Method B).

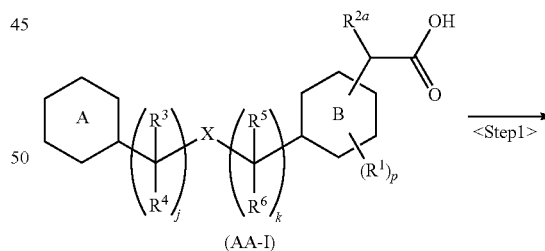
<Step 3>

The compound of Formula (Z-II) is subjected to substitution reaction with a compound of Formula (B-V). The compound of Formula (V-II) can be produced by reaction in a similar manner to that in <Step 4> in (Production Method B).

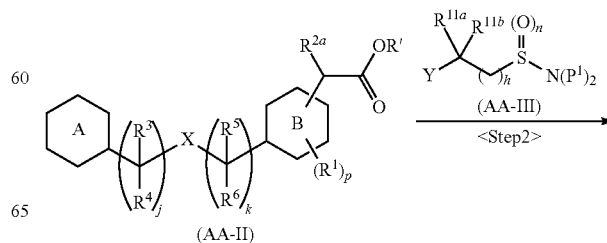
In Formula (I) above, Formulae (I)-1b, (I)-1c, (I)-1d, (I)-1e, and (I)-1f include optical isomers. The isomers can be separated through optical resolution using chiral column chromatography, preferential crystallization using an optically active salt, or asymmetric synthesis by a person skilled in the art based on conventional techniques.

<Production Method AA>

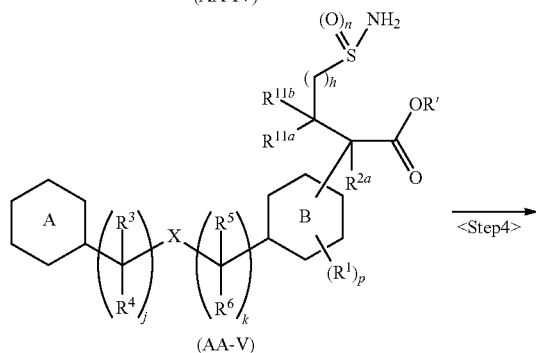
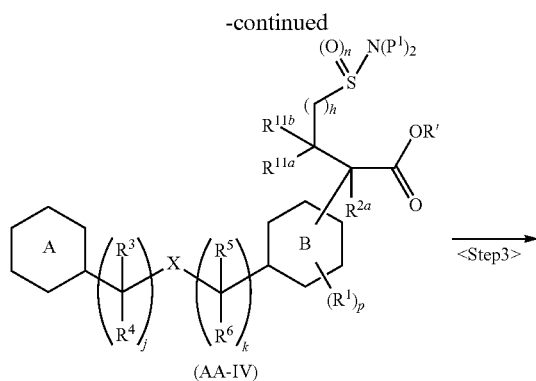
<When n=1, 2>



55



233



<Step 1>

A compound of Formula (AA-II) can be produced in a similar manner to that in <Step 2> in (Production Method B) by reacting a compound of Formula (AA-I), which is known in the art or can be easily produced from a known compound (for example, a phenylacetic acid derivative such as 4-hydroxy- α -methylphenylacetic acid (manufactured by Tokyo Chemical Industry Co., Ltd.) when the ring B is a benzene ring, or 2,3-dihydro-6-hydroxy-3-benzofuran acetic acid, 3,4-dihydro-7-hydroxy-2H-1-benzopyran-4-acetic acid, 2,3-dihydro-6-hydroxy-benzo[b]thiophene-3-acetic acid, and the like that can be produced in accordance with, for example, the method described in WO 2006/083781 pamphlet when the ring B is a bicyclic hetero ring such as a 2,3-dihydrobenzofuran ring, a 3,4-dihydro-2H-1-benzopyran ring, and a 2,3-dihydrobenzo[b]thiophene ring).

<Step 2>

The compound of Formula (AA-II) is subjected to substitution reaction. A compound of Formula (AA-IV) can be produced by causing the compound of Formula (AA-II) to react with a compound of Formula (AA-III) in a similar manner to that in <Step 5> in (Production Method X).

<Step 3>

The protective group P¹ in the compound of Formula (AA-IV) is deprotected. A compound of Formula (AA-V) can be

234

produced by causing the reaction of the compound of Formula (A-IV) in a similar manner to that in <Step 3> in (Production Method B).

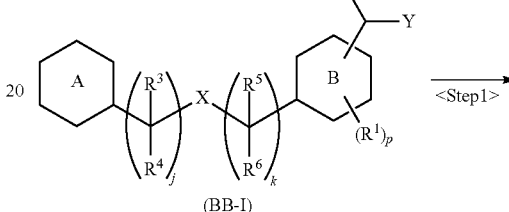
<Step 4>

The compound of Formula (AA-V) is subjected to ring formation reaction. A compound of Formula (I)-2a/Formula (I)-2c/Formula (I)-2f can be produced by reacting the compound of Formula (AA-V) in a similar manner to that in <Step 7> in (Production Method M).

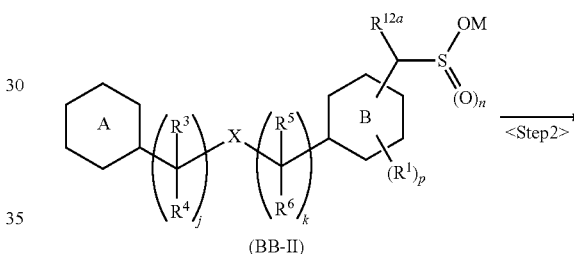
<Production Method BB>

<When n=2>

15



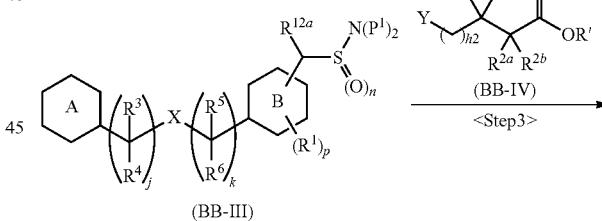
25



30

35

40



45

50

55

60

65

70

75

80

85

90

95

100

105

110

115

120

125

130

135

140

145

150

155

160

165

170

175

180

185

190

195

200

205

210

215

220

225

230

235

240

245

250

255

260

265

270

275

280

285

290

295

300

305

310

315

320

325

330

335

340

345

350

355

360

365

370

375

380

385

390

395

400

405

410

415

420

425

430

435

440

445

450

455

460

465

470

475

480

485

490

495

500

505

510

515

520

525

530

535

540

545

550

555

560

565

570

575

580

585

590

595

600

605

610

615

620

625

630

635

640

645

650

655

660

665

670

675

680

685

690

695

700

705

710

715

720

725

730

735

740

745

750

755

760

765

770

775

780

785

790

795

800

805

810

815

820

825

830

835

840

845

850

855

860

865

870

875

880

885

890

895

900

905

910

915

920

925

930

935

940

945

950

955

960

965

970

975

980

985

990

995

1000

1005

1010

1015

1020

1025

1030

1035

1040

1045

1050

1055

1060

1065

1070

1075

1080

1085

1090

1095

1100

1105

1110

1115

1120

1125

1130

1135

1140

1145

1150

1155

1160

1165

1170

1175

1180

1185

1190

1195

1200

1205

1210

1215

1220

1225

1230

1235

1240

1245

1250

1255

1260

1265

1270

1275

1280

1285

1290

1295

1300

1305

1310

1315

1320

1325

1330

1335

1340

1345

1350

1355

1360

1365

1370

1375

1380

1385

1390

1395

1400

1405

1410

1415

1420

1425

1430

1435

1440

1445

1450

1455

1460

1465

1470

1475

1480

1485

1490

1495

1500

1505

1510

1515

1520

1525

1530

1535

1540

1545

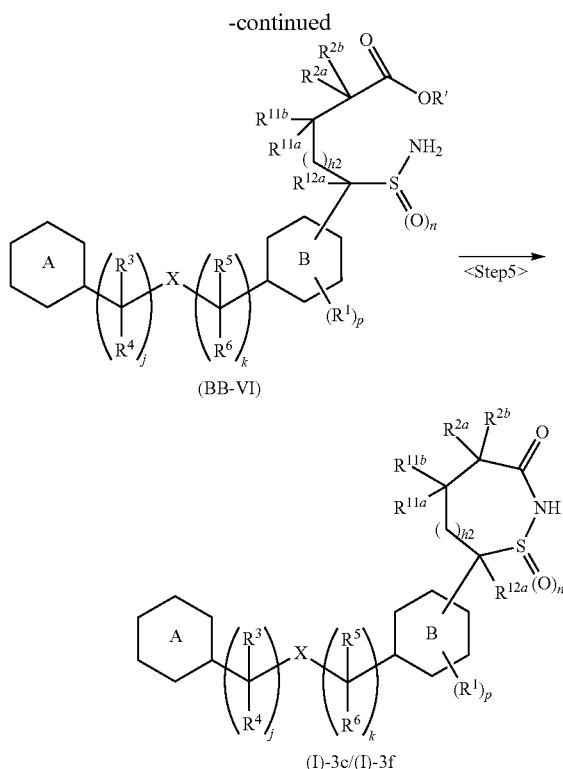
1550

1555

1560

1565

235



<Step 1>

A compound of Formula (BB-II) can be produced by reacting a compound of Formula (BB-I), which is known in the art or can be easily produced from a known compound (for example, a benzyl bromide derivative such as 4-(1-bromoethyl)-phenol when the ring B is a benzene ring, and 3-(bromomethyl)-6-hydroxy-2,3-dihydrobenzofuran that can be derived from 6-hydroxy-3 (2H)-benzofuran in accordance with a method known in a literature when the ring B is a bicyclic compound such as 2,3-dihydro-6-hydroxy-3-benzofuran ring), with a sulfur source such as sodium sulfite and potassium sulfite in a similar manner to that in <Step 3> in (Production Method U) (M is a metal such as Na and K in Formula (BB-II)).

<Step 2>

The compound of Formula (BB-II) is subjected to halogenation and sulfonylation, followed by sulfonamidation. A compound of Formula (BB-III) can be produced by causing the reaction of the compound of Formula (BB-II) in a similar manner to that in <Step 5> in (Production Method M).

<Step 3>

The compound of Formula (BB-III) is subjected to substitution reaction. A compound of Formula (BB-V) can be produced by causing the compound of Formula (BB-III) to react with a compound of Formula (BB-IV) in a similar manner to that in <Step 5> in (Production Method X).

<Step 4>

The protective group P¹ in the compound of Formula (BB-V) is deprotected. A compound of Formula (BB-VI) can be produced by causing the reaction of the compound of Formula (BB-V) in a similar manner to that in <Step 3> in (Production Method B).

<Step 5>

The compound of Formula (BB-VI) is subjected to ring formation reaction. A compound of Formula (I)-3c/Formula

236

(I)-3f can be produced by reacting the compound of Formula (BB-VI) in a similar manner to that in <Step 7> in (Production Method M).

[Concomitant Drug Containing Compound of the Present Invention]

The compound and pharmaceutical composition of the present invention can be used in combination with other drugs or medicines by a general method performed in medical practice. Particularly, such combination is used for the prevention, progress delay, and therapies of the mediating state of the GPR40 agonist, and is further particularly used against at least one disease selected from the group consisting of diabetes (Type 1 diabetes, Type 2 diabetes, and borderline type diabetes (impaired glucose tolerance (IGT) and/or impaired fasting glycemia (IFG))), insulin resistance, hyperinsulinemia, obesity, adiposity, and various diseases derived from or related to these diseases.

Examples of an insulin sensitizer and an anti-diabetic drug include 1) PPAR gamma agonists (specifically, pioglitazone, rosiglitazone, troglitazone, ciglitazone, darglitazone, englitazone, netoglitazone, etc.), 2) biguanide agents (specifically, metformin, buformin, phenformin, etc.), 3) sulfonylureas (specifically, tolbutamide, acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride, glipentide, gliquidone, glisohamide, tolazamide, etc.), 4) rapid-acting insulin secretagogues (specifically, nateglinide, mitiglinide, repaglinide, etc.), 5) alpha-glucosidase inhibitors (specifically, acarbose, voglibose, miglitol, camiglibose, adiposin, emiglitate, pradimicin Q, salbostatin, etc.), 6) insulin or insulin derivatives (specifically, insulin zinc suspensions, insulin lispro, insulin aspart, regular insulin, NPH insulin, insulin glargine, insulin detemir, mixed insulin, etc.), 7) GLP-1 or GLP-1 receptor agonists (specifically, exenatide, liraglutide, lixisenatide, taspoglutide, albiglutide, dulaglutide, etc.), 8) DPP-IV inhibitors (specifically, sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, teneligliptin, anagliptin, SYR-472, NVP-DPP-728, etc.), 9) alpha-2 antagonists (specifically, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, etc.), and 10) SGLT2 inhibitors (specifically, dapagliflozin, ipragliflozin, tofogliflozin, empagliflozin, canagliflozin, luseogliflozin, etc.). Examples of the insulin sensitizer and the anti-diabetic drug also include a combination drug (specifically, pioglitazone/metformin, pioglitazone/glimepiride, mitiglinide/voglibose, alogliptin/pioglitazone, alogliptin/metformin, etc.) containing as the components thereof, two or more drugs among the above drugs.

Examples of the insulin sensitizer and the anti-diabetic drug also include a hypolipidemic agent and a dyslipidemia therapeutic agent. Examples of the hypolipidemic agent and the dyslipidemia therapeutic agent include 1) omega-3 fatty acids (specifically, ethyl icosapentate (EPA-E preparation), docosahexaenoic acid (DHA), etc.), 2) HMG-CoA reductase inhibitors (specifically, atorvastatin, simvastatin, pitavastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, etc.), 3) HMG-CoA synthase inhibitors, 4) cholesterol absorption inhibitors (specifically, ezetimibe), 5) acyl-CoA-cholesterol acyltransferase (ACAT) inhibitors, 6) CETP inhibitors, 7) squalene synthase inhibitors, 8) antioxidants (specifically, probucol, etc.), 9) PPAR alpha agonists (specifically, clofibrate, etofibrate, fenofibrate, bezafibrate, ciprofibrate, gemfibrozil, KRP-101, etc.), 10) PPAR delta agonists, 11) LXR agonists, 12) FXR agonists (specifically, INT-747, etc.), 13) MTP inhibitors, 14) squalene epoxidase inhibitors, and 15) bile acid absorption inhibitors (specifically, cholestyramine, colestipol, etc.).

Examples of the insulin sensitizer and the anti-diabetic drug also include an anti-obesity agent. Specific examples of

the anti-obesity agent include 1) CB-1 receptor antagonists (specifically, rimonabant, SR-147778, BAY-65-2520, etc.), 2) monoamine reuptake inhibitors (specifically, sibutramine, mazindol, etc.), 3) serotonin reuptake inhibitors (specifically, fluoxetine, paroxetine, etc.), 4) lipase inhibitors (specifically, orlistat, cetilistat, etc.), 5) neuropeptide Y (NPY) receptor antagonists (specifically, S-2367, etc.), 6) peptide YY (PYY) receptor antagonists, and 7) adrenergic beta-3 receptor agonists (specifically, KRP-204, TRK-380/TAC-301, etc.).

The therapies can be performed in combination with not only other drugs, but also other therapies. Examples of the therapies include the improvement of lifestyle through weight control, exercise therapy, and diet therapy, and radiotherapy.

Against GPR40-involving diseases except for diabetes and obesity, the therapies can be performed in combination with drugs used in the respective fields.

Preferred examples of the concomitant drug include PPAR gamma agonists (more preferably pioglitazone, rosiglitazone), biguanide agents (more preferably metformin, buformin), sulfonyl urea agents (more preferably glibenclamide, gliclazide, glimepiride), rapid-acting insulin secretagogues (more preferably nateglinide, mitiglinide, repaglinide), alpha-glucosidase inhibitors (more preferably acarbose, voglibose, miglitol), insulin or insulin derivatives, GLP-1 or GLP-1 receptor agonists (more preferably exenatide, liraglutide), and DPP-IV inhibitors (more preferably sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, teneligliptin; further preferably sitagliptin, vildagliptin, alogliptin, linagliptin).

The combined use of the concomitant drug and conventional drugs against the diseases described above enables the dosage of the conventional drugs to be reduced, which can reduce the side effects of the conventional drugs. Needless to say, the combining method using the drugs is not limited to the diseases, and the drugs to be used in combination are not limited to the compounds exemplified above.

To use the compound of the present invention in combination with the drug to be used in combination, they may be individual preparations or be a drug combination. In the form of individual preparations, the compound and the drug can be taken at the same time or can be administered at different times.

[Producing Preparations of Prophylactic or Therapeutic Agents of the Present Invention]

The medicines of the present invention are administered in the form of pharmaceutical compositions.

The pharmaceutical compositions of the present invention may include at least the compound of Formula (I) or Formula (II) of the present invention and are produced in combination with pharmaceutically acceptable additives. More in detail, various dosage forms can be prepared by appropriately combining the compound of the present invention and, for example, excipients (for example, lactose, white soft sugar, mannitol, microcrystalline cellulose, silicic acid, corn starch, and potato starch), bonding agents (for example, celluloses (hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), microcrystalline cellulose, saccharide (lactose, mannitol, white soft sugar, sorbitol, erythritol, and xylitol), starches (corn starch and potato starch), gelatinized starch, dextrin, polyvinylpyrrolidone (PVP), macrogol, polyvinyl alcohol (PVA)), lubricants (for example, magnesium stearate, calcium stearate, talc, and carboxymethylcellulose), disintegrants (for example, starches (corn starch and potato starch), sodium carboxymethyl starch, carmellose, carmellose calcium, croscarmellose sodium, and crospovidone), coating agents (for example, celluloses (hydroxypropylcellu-

lose (HPC), hydroxypropylmethylcellulose (HPMC), aminoalkylmethacrylate copolymers E, and methacrylic copolymers LD), plasticizers (for example, triethyl citrate and macrogol), masking agents (for example, titanium oxide), colorants, flavoring agents, antiseptics (for example, benzalkonium chloride and p-hydroxybenzoate esters), tonicity agents (for example, glycerin, sodium chloride, calcium chloride, mannitol, and dextrose), pH regulators (for example, sodium hydroxide, potassium hydroxide, sodium carbonate, hydrochloric acid, sulfuric acid, and buffer solutions such as phosphate buffer solutions), stabilizing agents (for example, sugar, sugar alcohol, and xanthan gum), dispersants, antioxidants (for example, ascorbic acid, butylated hydroxyanisole (BHA), propyl gallate, and dl-alpha-tocopherol), buffer agents, preservatives (for example, paraben, benzyl alcohol, and benzalkonium chloride), perfumes (for example, vanillin, 1-menthol, and rose oil), solubilizing agents (for example, polyoxyethylene hydrogenated castor oil, polysorbate 80, polyethylene glycol, phospholipid cholesterol, and triethanolamine), absorbefacients (for example, sodium glycolate, sodium edetate, sodium caprate, acylcarnitines, and limonene), gelators, suspending agents, emulsifiers, and generally used suitable additives and solvents.

Examples of the various dosage forms include tablets, capsules, granules, powderer, pills, aerosols, inhalants, ointments, adhesive patches, suppositories, injections, troches, liquids, spirits, suspensions, extracts, and elixirs. The dosage forms can be administered to patients through oral administration, subcutaneous injection, intramuscular injection, intranasal administration, transdermal administration, intravenous injection, intraarterial injection, perineural administration, epidural administration, administration in subdural cavity, intraventricular administration, rectal administration, inhalation, or the like.

The dosage of the compound of the present invention is generally, 0.005 mg to 3.0 g, preferably, 0.05 mg to 2.5 g, and more preferably, 0.1 mg to 1.5 g per day for adults, but can be reduced or increased as needed depending on symptoms or administration routes.

The compound can be administered as a whole at once or be separately administered by being divided into two to six doses through oral administration or parenteral administration, or can be administered through repeated administration such as intravenous infusion.

The present specification incorporates, as references, the whole publications cited in the present specification, for example, related-art documents, publications of unexamined applications, patent publications, and other patent documents.

PHARMACOLOGICAL TEST EXAMPLES

The present invention is specifically described below with reference to test examples but is not limited to them.

The following pharmacological test examples 1 to 7 provide methods for investigating the efficacy of the compound of the present invention.

Pharmacological Test Example 1

Agonist Action on GPR40 of Human Origin

A CHO cell strain stably expressing GPR40 of human origin was used to determine the agonist action of a title compound. This cell strain was seeded in a clear bottom 96 well plate at 2×10^4 cells/100 μ L/well. The cell strain was cultured in a CO₂ incubator overnight using a Ham's F-12

239

medium containing a 10% fetal bovine serum, 100 U/mL penicillin, 0.1 mg/mL streptomycin, and 400 µg/mL Geneticin. Calcium 4 Assay Kit (Molecular Devices) was used as a fluorescent calcium indicator. One mL of 77 mg/mL probenecid (Invitrogen) was added to 100 mL of a calcium indicator solution to prepare a solution (loading solution) mixed with a 20 mM HEPES-containing Hanks' balanced salt solution (HBSS) in equal proportions. To the cells from which the culture solution was removed, 200 µL of the loading solution was added, and the cells were cultured in a CO₂ incubator for 1 hour. The title compound was diluted with a 20 mM HEPES-containing HBSS and was added to the cells by 50 µL, and the fluctuation of the Ca²⁺ concentration was measured by an intracellular ion analyzer. The EC₅₀ value of the title compound was calculated using the dose-response curve of fluorescence intensity variation. Table 1 indicates the compound of the present invention having an EC₅₀ value of less than 0.3 µM as A and the compound of the present invention having an EC₅₀ value of 0.3 µM or more and less than 3 µM as B.

Compound of Examples	EC ₅₀ values
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A
15	B
16	A
17	A
18	B
19	A
20	B
21	A
22	A
23(A)-a	A
23(A)-b	B
24(A)-a	A
24(A)-b	A
25(A)-a	A
25(A)-b	A
26	A
27	A
28	B
29	A
30	A
31	A
32	A
33	A
34	A
35	A
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	A
44	A
45	A
46	A
47	A
48	A
49	A
50	A

240

-continued

Compound of Examples	EC ₅₀ values
51(A)-a	A
51(A)-b	A
52(A)-a	A
52(A)-b	A
53(A)-a	A
53(A)-b	A
54(A)-a	A
54(A)-b	A
55(A)-a	A
55(A)-b	A
57	A
58	A
59	A
60	A
61	A
62	A
63	A
64	A
65	A
66	A
67	A
68	A
69	A

Pharmacological Test Example 2

Oral Glucose Tolerance Test

A reduction of blood glucose excursion of a subject compound after glucose load is examined using male C57BL/6J mice or SD rats fasted overnight. The subject compound is suspended with a solvent (for example, 0.5% carboxymethylcellulose) and is orally administered before glucose load. The solvent is singly administered to the control group. Blood specimen collection is performed before compound administration (pre-administration blood collection), after compound administration and immediately before glucose load, during glucose load, after 15, 30, 60, and 120 minutes, and the blood glucose level of the collected blood is measured. The reduction of blood glucose excursion is obtained by orally administering a dosage of 0.3 to 10 mg/kg of the preferable compound of the compound of the present invention.

Pharmacological Test Example 3

Solubility Test

(1) DMSO Precipitation Solubility (Kinetic Solubility)

A 10 mM DMSO solution of the compound of the present invention is added to a 50 mM phosphate buffer solution (pH 7.4) to the final concentration of 100 µM. The resultant solution is incubated with stirring at 600 rpm for 1.5 hours at room temperature, and then is filtered through a filter plate (4 µm, MultiScreen Solubility Filter Plate, Millipore). The absorbance of the obtained filtrate is measured at the maximum absorption wavelength using a plate reader (Powerscan HT, (Dainippon Pharmaceutical)). In this process, DMSO solutions of known concentration of the test compound (1, 3, 10, 30, and 100 µM) are prepared as standard solutions for a calibration curve. The absorbance of each of the standard solutions is measured to generate a calibration curve. The solubility (µM) of the compound is calculated using the absorbance values of the filtrate and the standard solutions.

(2) Crystal Solubility (Thermodynamic Solubility)

The compound of the present invention is added to water so as to be 1 mg/mL. The resultant solution is incubated at 37°C.

241

for 24 hours, and then is centrifuged. The obtained supernatant is analyzed by HPLC to detect the peak at the maximum absorption wavelength, and thus, the peak area is calculated. Similarly, DMSO solutions of known concentration of the test compound (0.03, 0.1, 0.3, 1, 3, and 10 $\mu\text{g/mL}$) are added as standard solutions for a calibration curve. The peak area of each of the standard solutions is measured. The solubility ($\mu\text{g/mL}$) of the compound is calculated using the peak areas of the obtained calibration curve.

Pharmacological Test Example 4

Metabolic Stability Test

The 10 mM DMSO solution of the compound of the present invention is added to a solution containing liver microsomes (human, mouse, or rat; XenoTech) and a NADPH generating systems (water containing beta-NADP, Glucose-6-Phosphate, G-6-PDH(Y), and MgCl_2) to the final concentration of 1 μM . The resultant solution is incubated at 37° C. for 20 minutes, and then the reaction is terminated by adding acetonitrile. Similarly, samples are collected at predetermined times during the incubation, and then the reaction is terminated. Each reaction solution is filtrated by centrifugation using a filter plate (MultiScreen HTS-HV plate, Millipore). The test compound in the filtrate is measured by high performance liquid chromatogram/mass spectrometry. Similarly, a sample with a reaction time of 0 is measured as a control. The compound concentration of the control is regarded as 100%, and the residual ratio of the compound in each reaction solution is calculated. These residual ratios are plotted with respect to the time, and the metabolic clearance ($\mu\text{L/mg/min}$) is calculated from the slope of the obtained regression line.

Pharmacological Test Example 5

hERG Inhibition Test by Patch-Clamp Technique

An effect against a human ether-a-go-go related gene (hERG) channel is measured using a fully automatic patch-clamp system (Patchliner (Nanion)). To confirm the hERG I_{Kr} current of a cell (hERG-HEK (Upstate)), the membrane potential is kept at -80 mV, and a depolarizing pulse is applied to the cell on a regular basis. After the generated current became stable, a test compound is added. The effect of the test compound against the hERG channel is confirmed from the change in tail current induced by a repolarizing pulse at -40 mV for 0.5 second subsequent to a depolarizing pulse at 40 mV for 0.5 second. The stimulation is performed at a frequency of once every 10 seconds. The measurement is performed at room temperature. The hERG channel inhibition rate is calculated as the reduction rate (suppression rate) of a tail current two minutes after the application of the test compound relative to the maximum tail current before the application.

The calculated suppression rate shows the possibility that drug-induced QT prolongation followed by fatal side effects (such as ventricular tachycardia and sudden death).

Pharmacological Test Example 6

Pharmacokinetics Study (Cassette Dosing PK)

The compound of the present invention is orally administered in a single dose to T- or 8-week-old male C57BL/6J Jcl mice or SD rats at 1 mg/kg (the vehicle is DMSO:Tween

242

80:ultrapure water=1:1:8 and 10 mL/kg). After the administration, the blood of the mouse is collected from the abdominal aorta after 0.25, 0.5, 1, and 2 hours, and the blood of the rat is collected from the jugular vein after 0.5, 1, 2, and 4 hours. The blood is centrifuged (3000 rpm, 15 minutes, and 4° C.) to obtain plasma, and the test compound in the plasma is measured by high performance liquid chromatogram/mass spectrometry. Similarly, standard solutions of known concentration of the test compound (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1 $\mu\text{g/mL}$) are measured to generate a calibration curve. The concentration ($\mu\text{g/mL}$) of the compound in the plasma is calculated using the calibration curve, and the maximum concentration in the plasma is indicated by C_{max} ($\mu\text{g/mL}$).

Pharmacological Test Example 7

Safety Assessment Study

The compound of the present invention is orally administered in a single dose to mice or rats. No death is confirmed and no noticeable behavior disorder is observed, and therefore the safety of the compound of the present invention is shown.

Pharmacological Test Example 8

Brain Penetration Study

Rats (male, SD, 7-9 weeks) are given single oral dose of invention compounds at 1 mg/10 mL/kg (solvent: 0.5% CMC) after overnight fasting. Blood samples are collected from jugular vein at 1 h after the administration and centrifuged (3,000 rpm, 15 min, 4° C.) to give plasma.

Cerebral cortexes are obtained at the same time points as for blood samples.

Plasma concentrations ($\mu\text{g/mL}$) of invention compounds are measured by LC-MS/MS and quantitated using standard solution (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 $\mu\text{g/mL}$) treated as well as invention compounds samples.

Cerebral cortexes are homogenized with water, and after addition of methanol they are mixed and centrifuged (14,000 rpm, 10 min, 4° C.) to give supernatants for measuring by LC-MS/MS.

Cerebral cortex concentrations ($\mu\text{g/mL}$) of invention compounds are measured by LC-MS/MS and quantitated using standard solution (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 $\mu\text{g/mL}$) treated as well as invention compounds samples.

Brain-to-plasma ratio (B/P ratio) of invention compound is calculated from plasma and cerebral cortex concentrations ($\mu\text{g/mL}$). B/P ratio is a good and common parameter for assessing extent of brain penetration, therefore it is possible to compare the extent of brain penetration among the invention compounds.

As a result, the compound of the present invention showed an excellent GPR40 agonist action and reduced blood glucose excursion in the single oral dose glucose tolerance test using normal mice or rats. In the safety assessment study, no abnormality to indicates low toxicity of the compound of the present invention.

By performing the tests described above, the compound of the present invention is confirmed to have favorable properties in at least one regard, such as solubility, metabolic stability, pharmacokinetics, the avoidance of an hERG channel inhibition action, and penetration through blood-brain barrier.

Accordingly, the compound of the present invention is expected to be used as a GPR40 agonist for insulin secretion.

243

gogues and prophylactic and/or therapeutic agents against diabetes (particularly, Type 2 diabetes or borderline type diabetes), obesity, and adiposity.

PREPARATION EXAMPLE

Hereinafter, Examples of the pharmaceutical compositions of the present invention are described.

Preparation Example 1

Tablet

Compound of Example 2	100 g
Lactose	137 g
Crystalline cellulose	30 g
Hydroxypropylcellulose	15 g
Sodium carboxymethyl starch	15 g
Magnesium stearate	3 g

The above components are weighed and then are uniformly mixed. The mixture is formed into tablets having a weight of 150 mg.

Preparation Example 2

Film Coating

Hydroxypropylmethylcellulose	9 g
Macrogol 6000	1 g
Titanium oxide	2 g

The above components are weighed. Subsequently, hydroxypropylmethylcellulose and macrogol 6000 are dissolved into water to disperse titanium oxide. The resultant liquid is film-coated on 300 g of the tablets of Preparation Example 1 to obtain film-coated tablets.

Preparation Example 3

Capsules

Compound of Example 6	50 g
Lactose	435 g
Magnesium stearate	15 g

The above components are weighed and then are uniformly mixed. Adequate hard capsules are each filled with 300 mg of the mixture by weight with a capsule inserter to produce capsules.

Preparation Example 4

Capsules

Compound of Example 8	100 g
Lactose	63 g
Corn starch	25 g
Hydroxypropylcellulose	10 g
Talc	2 g

244

The above components are weighed, and then the compound of Example 8, lactose, and corn starch are uniformly mixed. A hydroxypropylcellulose aqueous solution is added to the resultant mixture to produce granules by wet granulation. Talc is uniformly mixed with the granules, and adequate hard capsules are each filled with 200 mg of the mixture by weight to produce capsules.

Preparation Example 5

Powders

Compound of Example 11	200 g
Lactose	790 g
Magnesium stearate	10 g

The above components are weighed and then are uniformly mixed to produce 20% powdered drugs.

Preparation Example 6

Granules and Fine Granules

Compound of Example 13	100 g
Lactose	200 g
Crystalline cellulose	100 g
Partially gelatinized starch	50 g
Hydroxypropylcellulose	50 g

The above components are weighed, and the compound of Example 13, lactose, crystalline cellulose, and partially pregelatinized starch are uniformly mixed. A hydroxypropylcellulose (HPC) aqueous solution is added to the resultant mixture to produce granules or fine granules by wet granulation. The granules or fine granules are dried to be formulation of granules or fine granules.

EXAMPLES

Next, in order to describe the present invention further in detail, there are described Examples which should not be construed as limiting the scope of the present invention.

For the measurement of the nuclear magnetic resonance spectrum (NMR), JEOL JNM-ECX400 FT-NMR (manufactured by JEOL Ltd.) and JEOL JNM-ECX300 FT-NMR (manufactured by JEOL Ltd.) were used. As the LC-MS, a Waters Fraction Lynx MS system (manufactured by Waters Corporation) was used and as the column, a Sun Fire column (4.6 mm×5 cm, 5 μ m) (manufactured by Waters Corporation) was used. As a mobile phase, methanol:0.05% acetic acid aqueous solution=1:9 (0 min) to 10:0 (5 min) to 10:0 (7 min) (gradient condition) or methanol:0.05% trifluoroacetic acid aqueous solution=1:9 (0 min) to 10:0 (5 min) to 10:0 (7 min) (gradient condition) was used. As the UPLC/MS, a Waters UPLC-ZQ MS system (manufactured by Waters Corporation) was used and as the column, MGIII-H (2.1 mm×5 cm, 3 μ m) (manufactured by Shiseido Co. Ltd.) was used. As a mobile phase, methanol:0.05% trifluoroacetic acid aqueous solution=5:95 (0 min) to 100:0 (1 min) to 100:0 (2 min) (gradient condition) was used. For the preparative isolation system, gradient conditions appropriately changed depending on the type of the compound were used. In the present invention, in the preparative chromatography of a mixture of optical isomers of 5-substituted-isothiazol-3-ol 1-oxides [for

245

example, (Example 1) <Step 5>], an enantiomer having a shorter elution time is expressed as A and an enantiomer having a longer elution time is expressed as B, and in the preparative chromatography of a mixture of optical isomers of 5-substituted-1,2-thiazinan-3-one 1,1-dioxides, an enantiomer having a shorter elution time is expressed as C and an enantiomer having a longer elution time is expressed as D [for example, (Example 40) <Step 1>].

In the preparative chromatography of a mixture of optical isomers, a diastereomer having a shorter elution time is expressed as a and a diastereomer having a longer elution time is expressed as b [for example, (Example 23) <Step 6>]. In Structural Formulae of the compounds described below, a mark * is affixed to an asymmetric center of the enantiomer A, a mark C or D is affixed to an asymmetric center of the enantiomer C or D, and a mark a or b is affixed to an asymmetric center of a diastereomer a or b.

Reference Example 1

Synthesis of 4-hydroxyphenylboronic acid
N-methyliminodiacetic acid ester

A suspension of 4-hydroxyphenylboronic acid (10.3 g) and N-methyliminodiacetic acid (11.0 g) in dimethyl sulfoxide (37 mL)-toluene (333 mL) was heated and refluxed for 1.5 hours. From the resultant reaction mixture, toluene was distilled off under reduced pressure and the reaction mixture was poured into water (400 mL). The resultant reaction mixture was stirred for 1.5 hours. The precipitate was filtered, washed with water, and then dried under reduced pressure to give the title compound (16.4 g) as a gray white solid.

Reference Example 2

Synthesis of 3'-(bromomethyl)-2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)-1,1'-biphenyl

Concentrated sulfuric acid (1.4 g) was added dropwise to 48% hydrobromic acid (15 mL) at room temperature and [2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]-[1,1'-biphenyl]-3-yl]methanol (25 g) synthesized in accordance with the method described in [WO 2008/001931 pamphlet] was divided into five portions and added to the mixture. The reaction mixture was stirred at 60° C. for 2.5 hours and 48% hydrobromic acid (3.3 mL) was added to the mixture. The mixture was further stirred for 1 hour at the same temperature. After the reaction mixture was allowed to cool, water was added to the reaction mixture. The mixture was extracted with ethyl acetate. The obtained organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (27 g) as a pale yellow solid.

Example 1

Synthesis of 5-[4-[3-[4-(2-ethoxyethoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one

<Step 1> Synthesis of
1-bromo-2,6-dimethyl-4-(2-ethoxyethoxy)benzene

In accordance with the method described in [WO 2005/063729 pamphlet, Reference Example 31], the title com-

246

pound (12.8 g) was obtained as a colorless oil from 4-bromo-3,5-dimethylphenol (10.0 g) and 2-chloroethyl ethyl ether (5.94 mL).

<Step 2> Synthesis of (3-(2,6-dimethyl-4-(2-ethoxyethoxy)phenyl)phenyl)methanol

To a mixed solution of the compound (6.40 g) obtained in (Example 1) <Step 1> and 3-(hydroxymethyl)phenylboronic acid (3.56 g) in 1,4-dioxane (70 mL)-water (7 mL), bis(dibenzylideneacetone)palladium (1.35 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos: 1.92 g), and potassium phosphate monohydrate (10.8 g) were sequentially added and the resultant reaction mixture was heated and stirred at 100° C. for 4 hours. To the reaction mixture, water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=80:20 to 75:25) to give the title compound (4.13 g) as a colorless oil.

<Step 3> Synthesis of 4-((3-(2,6-dimethyl-4-(2-ethoxyethoxy)phenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

To a solution of the compound (1.50 g) obtained in (Example 1) <Step 2>, the compound (1.49 g) obtained in (Reference Example 1), and tri-n-butylphosphine (1.48 mL) in tetrahydrofuran (50 mL), 1,1'-azobis(N,N-dimethylformamide) (1.03 g) was added under ice-cooling and the resultant reaction mixture was stirred at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (2.37 g) as a white amorphous solid.

<Step 4> Synthesis of 5-chloro-isothiazol-3-ol
1-oxide

To a suspension of 5-chloro-isothiazol-3-ol (31.8 g) in dichloromethane (640 mL), m-chloroperbenzoic acid (content 65%) (60.7 g) was added under ice-cooling and the resultant reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was filtered and then the filtrate was concentrated under reduced pressure. To the residue, dichloromethane was added and the precipitate was filtered off. The filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (eluent; n-hexane:ethyl acetate=67:33 to 60:40) to give the title compound (26.0 g) as a white solid.

<Step 5> Optical Resolution of
(Rac)-5-chloro-isothiazol-3-ol 1-oxide

Optical resolution of the compound (30.5 g) obtained in (Example 1) <Step 4> was conducted by preparative chromatography (column: CHIRALPAK AS-H (5 cm×25 cm) manufactured by Daicel Chemical Industries, Ltd., eluent; carbon dioxide:methanol=86:14 (V/V), flow rate: 200 g/second, detection: UV 238 nm) to give each enantiomer of the title compound.

Primary fraction (14.7 g, white solid, >99% ee, retention time 4.8 minutes (enantiomer A: Example 1-5 (A)))

247

Secondary fraction (14.1 g, white solid, >98% ee, retention time 5.3 minutes (enantiomer B: Example 1-5 (B)))

The optical purity and the retention time were determined under the following conditions.

Column: CHIRALPAK AD-H (0.46 cm×25 cm) (manufactured by Daicel Chemical Industries, Ltd.),

Eluent: methanol:acetic acid=100:0.1 (v/v),

Flow rate: 1.0 mL/min,

Detection: UV 282 nm,

Column temperature: 40° C.

Hereinafter, the compounds and derivatives of them synthesized using the enantiomer A (Example 1-5 (A)) obtained in (Example 1) <Step 5> is expressed as “name of the compound+(A)” and the compounds and derivatives of them synthesized using the enantiomer B (Example 1-5 (B)) obtained in (Example 1) <Step 5> is expressed as “name of the compound+(B)”.

<Step 6> Synthesis of 5-(4-((3-(2,6-dimethyl 4-(2-ethoxyethoxy)phenyl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide (A)

To a solution of the compound (0.20 g) obtained in (Example 1) <Step 3> in 1,4-dioxane (3.7 mL), a 1M sodium hydroxide aqueous solution (1.1 mL) was added and the resultant reaction mixture was stirred at room temperature for 1.5 hours. To the reaction mixture, the enantiomer A (Example 1-5 (A)) (74 mg) obtained in (Example 1) <Step 5>, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos: 31 mg), and palladium acetate (8.4 mg) were sequentially added and the resultant reaction mixture was heated and stirred at 90° C. for 3 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by LC/MS to give the title compound (9.2 mg) as a pale yellow amorphous solid.

<Step 7> Synthesis of 5-[4-[[3-[4-(2-ethoxyethoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

To a solution of the compound (50 mg) obtained in (Example 1) <Step 6> in absolute THF (1 mL), a solution of 1M L-Selectride in tetrahydrofuran (0.31 mL) was added at 0° C. and the resultant reaction mixture was stirred at the same temperature for 1.5 hours. To the reaction mixture, 1M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (4.6 mg) as a white solid. The obtained compound by the reduction in this step is a mixture of diastereomers having a new asymmetric center.

The compounds of Examples 2 to Example 4 below were synthesized by the same method or a similar method in Example 1 from each corresponding raw material through a corresponding substituted phenylboronic acid ester and further through a corresponding substituted isothiazole.

248

Example 2

5-[4-[[3-[4-(2-ethoxyethoxy)-3-fluoro-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

Example 3

5-[4-[[3-[3-fluoro-4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

Example 4

5-[4-[[3-[4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

Example 5

Synthesis of Optically Active 5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a and (A)-b

<Step 1> Synthesis of 5-(4-((3-(2,4-dimethyl-6-(3-methylsulfonyl)propoxy)pyridin-3-yl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide (A)

The title compound was synthesized by the same method or a similar method in <Step 1> to <Step 6> in (Example 1) from a corresponding raw material through a corresponding substituted phenylboronic acid ester.

<Step 2> Synthesis of 5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a and (A)-b

To a solution of the compound (200 mg) obtained in (Example 5) <Step 1> in absolute THF (6 mL), a solution of 1M L-Selectride in tetrahydrofuran (1.5 mL) was added at 0° C. and the resultant reaction mixture was stirred at the same temperature for 1 hour. To the reaction mixture, 1M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by LC/MS to give each diastereomer of the title compound.

Primary fraction (1.6 mg, pale yellow solid, retention time 5.25 minutes, diastereomer a: Example 5 (A)-a)

Secondary fraction (3.4 mg, pale yellow solid, retention time 5.32 minutes, diastereomer b: Example 5 (A)-b)

Hereinafter, for example, the mixture of diastereomers that are obtained by the reduction in Example 5 <Step 2> using the enantiomer A (Example 5-1 (A)) obtained in Example 5 <Step 1> can be separated into optically active diastereomers as shown in Example 5 <Step 2>. For example, when a resolution column is used, the primary fraction that is firstly eluted in the separation condition is expressed as “name of the compound+a” as a diastereomer a (Example 5 (A)-a) and the secondary fraction that is eluted later is expressed as “name of the compound+b” as a diastereomer b (Example 5 (A)-b).

249

For example, Example 5-1 (B), Example 5 (B)-a, and Example 5 (B)-b can similarly be obtained when the enantiomer B obtained in Example 1 <Step 5> is used in Example 5 <Step 1>.

The compound of Example 6 below was synthesized by the same method or a similar method in Example 5 from each corresponding raw material through a corresponding substituted phenylboronic acid ester and further through a corresponding substituted isothiazole.

Example 6

5-[[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a trifluoroacetic acid salt and (A)-b trifluoroacetic acid salt

Primary fraction (6.4 mg, colorless amorphous solid, retention time 5.72 minutes, diastereomer a: Example 6 (A)-a)

Secondary fraction (8.1 mg, colorless oil, retention time 5.77 minutes, diastereomer b: Example 6 (A)-b)

Example 7

Synthesis of 5-[[4-[[3-[4-(3-hydroxy-3-methylbutoxy)-2,5-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a and (A)-b

<Step 1> Synthesis of 3-hydroxy-5-(4-((4' (3-hydroxy-3-methylbutoxy)-2',5'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)isothiazole 1-oxide (A)

The title compound was synthesized by the same method or a similar method in <Step 1> to <Step 6> in (Example 1) from a corresponding raw material through a corresponding substituted phenylboronic acid ester.

<Step 2> Synthesis of 5-[[4-[[3-[4-(3-hydroxy-3-methylbutoxy)-2,5-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a and (A)-b

To a solution of the compound (100 mg) obtained in (Example 7) <Step 1> in absolute THF (3 mL), a solution of 1M L-Selectride in tetrahydrofuran (0.79 mL) was added at 0° C. and the resultant reaction mixture was stirred at the same temperature for 1.5 hours. To the reaction mixture, 1M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was separated and purified by LC/MS. Optical resolution of the resultant solid was conducted by preparative chromatography (column: CHIRAL-PAK IB (2 cm×25 cm) manufactured by Daicel Chemical Industries, Ltd., eluent; hexane:ethanol:trifluoroacetic acid=70:30:0.1 (V/V), flow rate: 17 mL/min) to give each diastereomer of the title compound. The retention times were determined by LC/MS.

Primary fraction (10 mg, colorless amorphous solid, retention time 6.20 minutes, diastereomer a: Example 7 (A)-a)

Secondary fraction (21 mg, colorless amorphous solid, retention time 6.10 minutes, diastereomer b: Example 7 (A)-b)

250

Example 8

Synthesis of 5-[[4-[[3-[4-(3-hydroxypropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of 1-bromo-4-(3-((tert-butyl dimethylsilyl)oxy)propoxy)-2,6-dimethylbenzene

In accordance with the method in (Example 1) <Step 1>, the title compound (7.60 g) was obtained as a colorless oil from 4-bromo-3,5-dimethylphenol (4.00 g) and 3-((tert-butyl dimethylsilyl)oxy)propyl bromide (5.55 g).

<Step 2> Synthesis of (3-(2,6-dimethyl-4-(3-(tert-butyl dimethyl silyl)oxy)propoxy)phenyl)phenyl methanol

In accordance with the method in (Example 1) <Step 2>, the title compound (1.34 g) was obtained as a brown oil from the compound (3.60 g) obtained in (Example 8) <Step 1>.

<Step 3> Synthesis of 4-((3-(4-(3-((tert-butyl dimethylsilyl)oxy)propoxy)-2,6-dimethylphenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

In accordance with the method in (Example 1) <Step 3>, the title compound (1.21 g) was obtained as a pale yellow amorphous solid from the compound (1.20 g) obtained in (Example 8) <Step 2>.

<Step 4> Synthesis of 5-(4-((3-(2,6-dimethyl-4-(3-hydroxypropoxy)phenyl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide (A)

To a solution of the compound (0.20 g) obtained in (Example 8) <Step 3> in 1,4-dioxane (3.2 mL), a 1M sodium hydroxide aqueous solution (0.9 mL) was added and the resultant reaction mixture was stirred at room temperature for 1.5 hours. To the reaction mixture, the enantiomer A (62 mg) obtained in (Example 1) <Step 5>, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos: 26 mg), and palladium acetate (7.1 mg) were sequentially added and the resultant reaction mixture was heated and stirred at 100° C. for 2 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was dissolved in ethanol (5.0 mL) and tetrahydrofuran (5.0 mL). To the solution, concentrated hydrochloric acid (4.1 mL) was added and the resultant reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture, a saturated aqueous sodium hydrogen carbonate was added to make the mixture weak acidic and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by LC/MS to give the title compound (23 mg) as a pale yellow amorphous solid.

<Step 5> Synthesis of 5-[[4-[[3-[4-(3-hydroxypropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

In accordance with the method in (Example 1) <Step 7>, the title compound (4.2 mg) was obtained as a pale yellow

251

amorphous solid from the compound (11 mg) obtained in (Example 8) <Step 4>. The title compound is a mixture of diastereomers.

The compounds of Example 9 to Example 10 below were synthesized by the same method or a similar method in Example 8 from each corresponding raw material through a corresponding substituted phenylboronic acid ester and further through a corresponding substituted isothiazole.

Example 9

5-[4-[[3-[4-[(2R)-2,3-dihydroxypropoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

Example 10

5-[4-[[3-[4-[3-hydroxy-2-(hydroxymethyl)propoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

Example 11

Synthesis of 5-[4-[[3-[4-(3-aminopropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one trifluoroacetic acid salt

<Step 1> Synthesis of
3-(4-bromo-3,5-dimethylphenoxy)propyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 1) <Step 3>, the title compound (6.6 g) was obtained as a white solid from 4-bromo-3,5-dimethylphenol (5.00 g) and (3-hydroxypropyl)carbamic acid tert-butyl ester (5.2 g).

<Step 2> Synthesis of 3-((3'-formyl-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 1) <Step 2>, the title compound (1.95 g) was obtained as a red oil from the compound (2.3 g) obtained in (Example 11) <Step 1> and 3-formylphenylboronic acid (0.95 g).

<Step 3> Synthesis of 3-((3'-hydroxymethyl-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)carbamic acid tert-butyl ester

The compound (1.84 g) obtained in (Example 11) <Step 2> was dissolved in a solution of tetrahydrofuran (12.0 mL) and methanol (6.0 mL). To the solution, sodium borohydride (0.18 g) was gradually added under ice-cooling. The reaction mixture was allowed to reach room temperature and stirred for 2 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added to make the mixture pH 7 and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography

252

(eluent; n-hexane:ethyl acetate=75:25 to 70:30) to give the title compound (1.73 g) as an amorphous solid.

<Step 4> Synthesis of 3-((2,6-dimethyl-3'-((4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)phenoxy)methyl-[1,1'-biphenyl]-4-yl)oxy)propyl)carbamic acid tert-butyl ester

In accordance with the method in Example 1 <Step 3>, the title compound (2.09 g) was obtained as a white amorphous solid from the compound (1.70 g) obtained in (Example 11) <Step 3>.

<Step 5> Synthesis of 3-((2,6-dimethyl-3'-((4-(1-oxide-3-oxo-2,3-dihydroisothiazol-5-yl)phenoxy)methyl-[1,1'-biphenyl]-4-yl)oxy)propyl)carbamic acid tert-butyl ester (A)

In accordance with the method in Example 1 <Step 6>, the title compound (45.6 mg) was obtained as a white amorphous solid from the compound (100 mg) obtained in (Example 11) <Step 4> using the enantiomer A (Example 1-5 (A)) obtained in (Example 1) <Step 5>.

<Step 6> Synthesis of 5-(4-((4'-(3-aminopropoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)isothiazol-3(2H)-one 1-oxide (A)

The compound (45 mg) obtained in (Example 11) <Step 5> was dissolved in ethyl acetate (1.0 mL). To the solution, a solution of 4M hydrogen chloride in ethyl acetate (1.0 mL) was added and the resultant reaction mixture was stirred at room temperature over night. The reaction mixture was concentrated under reduced pressure and dried to give the title compound (49 mg) as a yellow solid.

<Step 7> Synthesis of 5-[4-[[3-[4-[(3R)-3-hydroxybutoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

In accordance with the method in (Example 1) <Step 7>, the title compound (26 mg) was obtained as a colorless amorphous solid from the compound (50 mg) obtained in (Example 11) <Step 6>. The obtained compound is a mixture of diastereomers.

Example 12

Synthesis of 5-[4-[[3-[4-[(3R)-3-hydroxybutoxy]-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of (3R)-3-acetoxibutoxy 4-methylbenzenesulfonate

The hydroxy group in (3R)-3-hydroxybutoxy 4-methylbenzenesulfonate (35.0 g) that was synthesized in accordance with the method in [Tetrahedron: Asymmetry, vol. 5 (1), pp. 117-118 (1994)] was acetylated in a common procedure to give the title compound (15.6 g) as a yellow oil.

<Step 2> Synthesis of 4-((3R)-3-acetoxibutoxy)-1-bromo-2,6-dimethylbenzene

In accordance with the method in (Example 1) <Step 1>, the title compound (4.09 g) was obtained as a colorless oil

253

from 4-bromo-3,5-dimethylphenol (5.00 g) and the compound (7.83 g) obtained in (Example 12) <Step 1>.

<Step 3> Synthesis of (3-(4-((3R)-3-acetoxybutoxy)-2,6-dimethylphenyl)phenyl)methanol

In accordance with the method in (Example 1) <Step 2>, the title compound (1.36 g) was obtained as a brown oil from the compound (2.00 g) obtained in (Example 12) <Step 2>.

<Step 4> Synthesis of 4-((3-(4-((3R)-3-acetoxybutoxy)-2,6-dimethylphenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

In accordance with the method in (Example 1) <Step 3>, the title compound (1.83 g) was obtained as a white solid from the compound (1.20 g) obtained in (Example 12) <Step 3>.

<Step 5> Synthesis of 5-(4-((3-(2,6-dimethyl-4-((3R)-3-hydroxybutoxy)phenyl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide (A)

To a solution of the compound (0.40 g) obtained in (Example 12) <Step 4> in 1,4-dioxane (7.0 mL), a 1M sodium hydroxide aqueous solution (2.1 mL) was added and the resultant reaction mixture was stirred at room temperature for 1.5 hours. To the reaction mixture, the enantiomer A (137 mg) obtained in (Example 1) <Step 5>, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos: 57 mg), and palladium acetate (39 mg) were sequentially added and the resultant reaction mixture was heated and stirred at 100° C. for 2 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was dissolved in ethanol (5.0 mL). To the solution, a 1M sodium hydroxide aqueous solution (4.9 mL) was added and the resultant reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added to make the mixture weak acidic and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by LC/MS to give the title compound (29 mg) as a pale yellow amorphous solid.

<Step 6> Synthesis of 5-[4-[[3-[4-((3R)-3-hydroxybutoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

In accordance with the method in (Example 1) <Step 7>, the title compound (5.2 mg) was obtained as a pale yellow amorphous solid from the compound (11 mg) obtained in (Example 12) <Step 5>. The obtained compound is a mixture of diastereomers.

Example 13

Synthesis of 5-[4-[[3-[2,6-dimethyl 4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of (3-(2,6-dimethyl 4-((tert-butyl)dimethylsilyl)oxy)phenyl)phenyl)methanol

In accordance with the method in (Example 1) <Step 2>, the title compound (10.4 g) was obtained as an orange solid

254

from 1-bromo-4-((tert-butyl)dimethylsilyl)oxy)-2,6-dimethylbenzene (15.0 g) that was synthesized in accordance with the method described in [WO 2005/063729 pamphlet].

<Step 2> Synthesis of 4-((3-(2,6-dimethyl-4-((tert-butyl)dimethylsilyl)oxy)phenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

In accordance with the method in (Example 1) <Step 3>, the title compound (0.24 g) was obtained as a pale yellow amorphous solid from the compound (0.20 g) obtained in (Example 13) <Step 1>.

<Step 3> Synthesis of 4-((3-(2,6-dimethyl-4-hydroxyphenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

To a solution of the compound (4.18 g) obtained in (Example 13) <Step 2> in tetrahydrofuran (70 mL), a solution of 1M tetrabutylammonium fluoride in tetrahydrofuran (14.6 mL) was added under ice-cooling and the mixture was stirred under ice-cooling for 30 minutes. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=33:67 to 20:80) to give the title compound (1.06 g) as a beige amorphous solid.

<Step 4> Synthesis of 4-((3-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)phenyl)methoxy)phenylboronic acid N-methyliminodiacetic acid ester

In accordance with the method in (Example 1) <Step 1>, the title compound (79 mg) was obtained as a white solid from the compound (0.20 g) obtained in (Example 13) <Step 3> and 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (0.14 g) synthesized in accordance with the method described in [WO 2007/018314 pamphlet].

<Step 5> Synthesis of 5-(4-((3-(2,6-dimethyl 4-(3-(methylsulfonyl)propoxy)phenyl)phenyl)methoxy)phenyl)isothiazol-3-ol 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (15 mg) was obtained as a beige solid from the compound (76 mg) obtained in (Example 13) <Step 4> using the enantiomer A (Example 1-5 (A)) obtained in (Example 1) <Step 5>.

<Step 6> Synthesis of 5-[4-[[3-[2,6-dimethyl 4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)-a and (A)-b

In accordance with the method in (Example 7) <Step 2>, each diastereomer of the title compound was obtained from the compound (100 mg) obtained in (Example 13) <Step 5>. The separation condition was as follows. Preparative chromatography (column: CHIRALPAK IB (2 cm×25 cm) manufactured by Daicel Chemical Industries, Ltd., eluent; hexane: ethanol:trifluoroacetic acid=50:50:0.1 (V/V), flow rate: 17 mL/min). The retention times were determined by LC/MS. Primary fraction (7.8 mg, colorless amorphous solid, retention time 5.62 minutes, diastereomer a: Example 13 (A)-a)

255

Secondary fraction (6.0 mg, colorless amorphous solid, retention time 5.53 minutes, diastereomer b: Example 13 (A)-b)

Example 14

Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

<Step 1> Synthesis of 4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl carbamic acid tert-butyl ester

To a solution of (2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol (4.0 g), 4-hydroxycarbamic acid tert-butyl ester (5.91 g), and tri-n-butylphosphine (6.97 mL) in tetrahydrofuran (80 mL), 1,1'-azobis(N,N-dimethylformamide) (4.87 g) was added under ice-cooling and the resultant reaction mixture was stirred at room temperature for 62 hours. The precipitated solid was filtered off and the solvent in the filtrate was distilled off under reduced pressure. To the resultant residue, water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=95:5) twice to give the title compound (6.17 g) as a colorless amorphous solid.

<Step 2> Synthesis of 4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)aniline

The compound (6.15 g) obtained in (Example 14) <Step 1> was dissolved in ethyl acetate (27 mL). To the solution, a solution of 4M hydrogen chloride in ethyl acetate (19 mL) was added and the resultant reaction mixture was stirred at room temperature over night. The reaction mixture was diluted with ethyl acetate. To the mixture, a saturated aqueous sodium hydrogen carbonate solution was added to make the mixture basic and the mixture was extracted with ethyl acetate. The obtained organic phase was washed with brine and then dried over anhydrous sodium sulfate. The organic phase was concentrated under reduced pressure to give the title compound (4.58 g) as a pale brown oil.

<Step 3> Synthesis of tert-butyl

2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)acetate

To a solution of the compound (0.50 g) obtained in (Example 14) <Step 2> in N,N'-dimethylformamide (3.3 mL), diisopropylethylamine (0.57 mL) and tert-butyl 2-bromoacetate (0.23 mL) were sequentially added and the resultant reaction mixture was stirred at 60° C. for 4 hours. The reaction mixture was allowed to reach room temperature, then diluted with water, and extracted with ethyl acetate. The obtained organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=90:10) to give the title compound (0.60 g) as a pale yellow oil.

256

<Step 4> Synthesis of tert-butyl

2-((N-(tert-butoxycarbonyl)sulfamoyl)(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)acetate

To a solution of tert-butanol (0.14 mL) in methylene chloride (0.70 mL), chlorosulfonyl isocyanate (0.13 mL) was added under ice-cooling. The resultant reaction mixture was stirred at room temperature for 30 minutes to prepare a solution of chlorosulfonyl carbamic acid tert-butyl ester in methylene chloride. The mixed solution was added to a solution of the compound (0.30 g) obtained in (Example 14) <Step 3> and diisopropylethylamine (0.38 mL) in methylene chloride (0.70 mL) under ice-cooling and the resultant reaction mixture was stirred at room temperature for 4 hours. The reaction solution was diluted with water and extracted with methylene chloride. The obtained organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give a mixture (0.48 g) containing the title compound as a colorless amorphous solid.

<Step 5> Synthesis of 2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(sulfamoyl)amino)acetic acid

To a solution of the compound (0.30 g) obtained in (Example 14) <Step 4> in methylene chloride (3.0 mL), trifluoroacetic acid (0.8 mL) was added under ice-cooling and the resultant reaction mixture was stirred at room temperature for 21 hours. To the reaction solution, water was added and the mixture was extracted with methylene chloride. The obtained organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (0.20 g) as a brown amorphous solid.

<Step 6> Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

To a solution of the compound (80.0 mg) obtained in (Example 14) <Step 5> in tetrahydrofuran (1.2 mL), 1-hydroxybenzotriazole monohydrate (27.8 mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSC-HCl: 34.8 mg) were sequentially added and the resultant reaction mixture was stirred at room temperature for 10 minutes. Subsequently, triethylamine (27.84 µl) was added and the resultant reaction mixture was stirred at room temperature for 15 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. To the residue, ethyl acetate was added. The mixture was sequentially washed with 1M hydrochloric acid and brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative TLC (eluent; methylene chloride:methanol=20:1, 1% acetic acid). The obtained compound was triturated with ether to give the title compound (10.2 mg) as a brown solid.

257

Example 15

Synthesis of 5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

<Step 1> Synthesis of 4-((2',6'-dimethyl-4'-(3-methylsulfonyl)propoxy-[1,1'-biphenyl]-3-yl)methoxy)phenyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 14) <Step 1>, the title compound (1.54 g) was obtained as a white amorphous solid from {2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]-[1,1'-biphenyl]-3-yl}methanol (1.0 g) that was synthesized in accordance with the method described in [WO 2008/001931 pamphlet].

<Step 2> Synthesis of 4-((2',6'-dimethyl-4'-(3-methylsulfonyl)propoxy-[1,1'-biphenyl]-3-yl)methoxy)aniline

In accordance with the method in (Example 14) <Step 2>, the title compound (1.18 g) was obtained as a pale yellow oil from the compound (1.53 g) synthesized in (Example 15) <Step 1>.

<Step 3> Synthesis of ethyl 2-((4-((2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)acetate

In accordance with the method in (Example 14) <Step 3>, the title compound (0.40 g) was obtained as a pale yellow oil from the compound (0.40 g) obtained in (Example 15) <Step 2> and ethyl 2-bromoacetate (95.6 µl).

<Step 4> Synthesis of ethyl 2-((N-(tert-butoxycarbonyl)sulfamoyl)(4-((2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)acetate

In accordance with the method in (Example 14) <Step 4>, the title compound (0.55 g) was obtained as a brown amorphous solid from the compound (0.38 g) obtained in (Example 15) <Step 3>.

<Step 5> Synthesis of ethyl 2-((4-((2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]-[1,1'-biphenyl]-3-yl)methoxy)phenyl)sulfamoyl)amino)acetate

In accordance with the method in (Example 14) <Step 5>, the title compound (0.47 g) was obtained as a brown amorphous solid from the compound (0.53 g) obtained in (Example 15) <Step 4>.

<Step 6> Synthesis of 5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

To a solution of the compound (0.20 g) obtained in (Example 15) <Step 5> in ethanol (0.80 mL), a 2M sodium hydroxide aqueous solution (0.33 mL) was added under ice-cooling and the resultant reaction mixture was stirred for 30 minutes. To the reaction solution, ethyl acetate and 1M hydrochloric acid were added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was dis-

258

tilled off under reduced pressure and the resultant residue was purified by LC/MS to give the title compound (17 mg) as a pale beige solid.

Example 16

Synthesis of 5-[2-chloro-4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

<Step 1> Synthesis of (2-chloro-4-hydroxyphenyl)carbamic acid tert-butyl ester

To a solution of 4-amino-3-chlorophenol hydrochloride (1.0 g) and triethylamine (0.77 mL) in tetrahydrofuran (4.6 mL), di-tert-butyl carbonate (1.39 mL) was slowly added dropwise and the resultant reaction mixture was heated and refluxed for 8 hours. The reaction mixture was allowed to reach room temperature and added to a saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give a mixture (1.42 g) containing the title compound as a pale brown solid.

<Step 2> Synthesis of (2-chloro-4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 14) <Step 1>, a mixture (0.83 g) containing the title compound was obtained as a colorless oil using the compound (0.69 g) obtained in (Example 16) <Step 1>.

<Step 3> Synthesis of 2-chloro-4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)aniline hydrochloride

To a solution of the compound (0.78 g) obtained in (Example 16) <Step 2> in ethyl acetate (3.0 mL), a solution of 4M hydrogen chloride in ethyl acetate (2.23 mL) was added and the resultant reaction mixture was stirred at room temperature for 3 hours. The precipitate was collected by filtration and dried under reduced pressure to give the title compound (0.47 g) as a white solid.

<Step 4> Synthesis of ethyl 2-((2-chloro-4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)acetate

In accordance with the method in (Example 14) <Step 3>, the title compound (357 mg) was obtained as a pale yellow oil using the compound (0.40 g) obtained in (Example 16) <Step 3> and ethyl 2-bromoacetate (0.24 mL).

<Step 5> Synthesis of ethyl 2-((2-chloro-4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)sulfamoyl)amino)acetate

In accordance with the methods in (Example 14) <Step 4> and (Example 14) <Step 5>, a mixture (839 mg) containing the title compound was obtained as a brown oil using the compound (0.34 g) obtained in (Example 16) <Step 4>.

259

<Step 6> Synthesis of 5-[2-chloro-4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

In accordance with the method in (Example 15) <Step 6>, the title compound (46 mg) was obtained as a pale brown amorphous solid using the compound (0.80 g) obtained in (Example 16) <Step 5>.

Example 17

Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]-2-methylphenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

<Step 1> Synthesis of (4-hydroxy-2-methylphenyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 16) <Step 1>, the title compound (1.71 g) was obtained as a pale brown amorphous solid using 4-amino-3-methylphenol (1.0 g).

<Step 2> Synthesis of (4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-methylphenyl)carbamic acid tert-butyl ester

In accordance with the method in (Example 16) <Step 2>, the title compound (0.70 g) was obtained as a colorless amorphous solid using the compound (0.40 g) obtained in (Example 17) <Step 1>.

<Step 3> Synthesis of 4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-methylaniline hydrochloride

In accordance with the method in (Example 16) <Step 3>, the title compound (0.47 g) was obtained as a white solid using the compound (0.65 g) obtained in (Example 17) <Step 2>.

<Step 4> Synthesis of ethyl 2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-methylphenyl)amino)acetate

In accordance with the method in (Example 16) <Step 4>, the title compound (0.31 g) was obtained as a brown oil using the compound (0.40 g) obtained in (Example 17) <Step 3>.

<Step 5> Synthesis of ethyl 2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-methylphenyl)(sulfamoyl)amino)acetate

In accordance with the method in (Example 16) <Step 5>, a mixture (895 mg) containing the title compound was obtained as a brown oil using the compound (0.30 g) obtained in (Example 17) <Step 4>.

<Step 6> Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]-2-methylphenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

In accordance with the method in (Example 15) <Step 6>, the title compound (27 mg) was obtained as a brown amorphous solid using the compound (0.85 g) obtained in (Example 17) <Step 5>.

260

Example 18

Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-4-methyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one

<Step 1> Synthesis of ethyl 2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)propionate

In accordance with the method in (Example 14) <Step 3>, the title compound (0.56 g) was obtained as an orange oil from a hydrochloride (0.50 g) of the compound obtained in (Example 14) <Step 2> and ethyl 2-bromopropionate (0.39 mL).

<Step 2> Synthesis of ethyl 2-((N-(tert-butoxycarbonyl)sulfamoyl)(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)amino)propionate

In accordance with the method in (Example 14) <Step 4>, a mixture (753 mg) containing the title compound was obtained as a brown amorphous solid using the compound (0.55 g) obtained in (Example 18) <Step 1>.

<Step 3> Synthesis of ethyl 2-((4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(sulfamoyl)amino)propionate

In accordance with the method in (Example 14) <Step 5>, a mixture (0.70 g) containing the title compound was obtained as a brown amorphous solid using the compound (0.74 g) obtained in (Example 18) <Step 2>.

<Step 4> Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-4-methyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one

In accordance with the method in (Example 15) <Step 6>, the title compound (5 mg) was obtained as a pale yellow solid using the compound (0.30 g) obtained in (Example 18) <Step 3>.

Example 19

Synthesis of 5-[4-[[3-[2,6-dimethyl 4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one

<Step 1> Synthesis of 5-(4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)isothiazol-3(2H)-one 1,1-dioxide

To a solution of the compound (50 mg) obtained in (Example 13) <Step 5> in methanol (5.0 mL), water (0.5 mL) and OXONE (registered trademark) (117 mg) were added and the resultant reaction mixture was stirred at 40° C. for 18 hours. Subsequently, the mixture was stirred at 100° C. for 23 hours. The reaction mixture was allowed to reach room temperature and water was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give a mixture (50.0 mg) containing the title compound as a colorless solid.

261

<Step 2> Synthesis of 5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one

In accordance with the method in (Example 1) <Step 7>, the title compound (6.0 mg) was obtained as a colorless solid using the compound (50 mg) obtained in (Example 19) <Step 1>. The obtained compound is a racemic mixture.

Example 20

Synthesis of 5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one

To a solution of the compound (50 mg) obtained in (Example 6) in acetone (5 mL), water (0.5 mL) and OXONE (registered trademark) (363 mg) were added and the resultant reaction mixture was stirred at 90° C. for 16 hours. The reaction mixture was allowed to reach room temperature and water was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol=20:1) to give the title compound (11 mg) as a colorless amorphous solid. The obtained compound is a racemic mixture.

Example 21

Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one

<Step 1> Synthesis of 4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzaldehyde

To a solution of (2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (1.0 g), 4-hydroxybenzaldehyde (0.58 g), and triphenylphosphine (1.48 g) in tetrahydrofuran (10 mL), a solution of 40% diisopropylazodicarboxylic acid diisopropyl in toluene (1.09 mL) was added under ice-cooling and the resultant reaction mixture was stirred under ice-cooling for 3 hours. A solution of diisopropyl azodicarboxylate in toluene (0.6 mL) was further added and the resultant reaction mixture was stirred at room temperature for 12 hours. From the reaction mixture, the solvent was distilled off under reduced pressure to give a residue and water was added to the resultant residue. The mixture was extracted with an organic solvent and the resultant organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-heptane:ethyl acetate=100:0 to 100:20) to give the title compound (1.2 g) as a colorless oil.

<Step 2> Synthesis of ethyl 3-amino-3-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)propionate

A mixed solution of the compound (1 g) obtained in (Example 21) <Step 1>, ammonium acetate (0.73 g), and monoethyl malonate (0.44 g) in ethanol (15 mL) was heated and refluxed for 20 hours. The reaction mixture was allowed to reach room temperature and a 2M sodium hydroxide aqueous solution was added. The mixture was extracted with ethyl acetate. The obtained organic phase was dried over anhydrous

262

sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-heptane:ethyl acetate=100:0 to 100:20) to give the title compound (0.28 g) as a yellow oil.

<Step 3> Synthesis of ethyl 3-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)-3-(sulfamoyl)propionate

In accordance with the method in (Example 14) <Step 4>, a mixture (8 mg) containing the title compound was obtained as a pale yellow amorphous solid using the compound (200 mg) obtained in (Example 21) <Step 2>.

<Step 4> Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one

In accordance with the method in (Example 15) <Step 6>, the title compound (3.2 mg) was obtained as a pale yellow solid using the compound (7.0 mg) obtained in (Example 21) <Step 3>. The title compound is a racemic mixture.

Example 22

Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

<Step 1> Synthesis of N,N-bis(4-methoxybenzyl)methanesulfonamide

To a solution of methanesulfonamide (5 g) in N,N-dimethylformamide (75 mL), potassium carbonate (29.1 g) was added and the resultant reaction mixture was stirred at room temperature for 5 hours. To the solution, p-methoxybenzyl chloride (18.1 g) was added and the resultant reaction mixture was stirred at room temperature for 19 hours. To the reaction solution, water was added and the mixture was extracted with ethyl acetate. The obtained organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (17.1 g) as a white solid.

<Step 2> Synthesis of 2-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)-N,N-bis(4-methoxybenzyl)ethanesulfonamide

To a solution of the compound (1.19 g) obtained in (Example 22) <Step 1> in tetrahydrofuran (5.5 mL), a solution of 1M lithium hexamethyldisilazide in tetrahydrofuran (8.29 mL) was added dropwise at -20° C. After stirring the mixture at -20° C. for 1 hour, a solution of diethyl chlorophosphate (0.51 mL) in tetrahydrofuran (3 mL) was added dropwise. After stirring the mixture at -20° C. for 1 hour, a solution of the compound (0.75 g) obtained in (Example 21) <Step 1> in tetrahydrofuran (3 mL) was added dropwise. After stirring the mixture at room temperature for 19 hours, 1M hydrochloric acid and water were sequentially added to the reaction solution and the mixture was extracted with ethyl acetate. The obtained organic phase was washed with brine and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=90:10 to 80:20) to give the title compound (890 mg) as a colorless oil.

263

<Step 3> Synthesis of dimethyl

2-(2-(N,N-bis(4-methoxybenzyl)sulfamoyl)-1-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)ethyl)malonate

To a solution of dimethyl malonate (0.54 g) in tetrahydrofuran (6 mL), a solution of 28% sodium methoxide in methanol (0.81 g) was added and the resultant reaction mixture was stirred for 1 hour. Subsequently, a solution of the compound (0.87 g) obtained in (Example 22) <Step 2> in tetrahydrofuran (4 mL) was added and the resultant reaction mixture was heated and refluxed for 17 hours. The reaction mixture was allowed to reach room temperature and a 10% citric acid aqueous solution was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and the resultant organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=85:15 to 70:30) to give the title compound (730 mg) as a white amorphous solid.

<Step 4> Synthesis of methyl 4-(N,N-bis(4-methoxybenzyl)sulfamoyl)-3-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)butanoate

To a solution of the compound (0.72 g) obtained in (Example 22) <Step 3> in N,N-dimethylformamide (6.0 mL), water (33.8 mg) and sodium chloride (54.92 mg) were added and the resultant reaction mixture was heated and refluxed for 2.5 hours. The reaction mixture was allowed to reach room temperature and water was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and the resultant organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=85:15 to 70:30) to give the title compound (358 mg) as a colorless oil.

<Step 5> Synthesis of methyl 3-(4-((2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)phenyl)-4-sulfamoylbutanoate

To a solution of the compound (0.32 g) obtained in (Example 22) <Step 4> in methylene chloride (3.0 mL), trifluoroacetic acid (0.60 mL) was added and the resultant reaction mixture was stirred at room temperature for 15 hours. The reaction solution was poured into a mixed solution of a 10% potassium carbonate aqueous solution and ethyl acetate and the mixture was extracted with ethyl acetate. The obtained organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=75:25 to 65:35) to give the title compound (150 mg) as a colorless oil.

<Step 6> Synthesis of 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

To a mixed solution of the compound (140 mg) obtained in (Example 22) <Step 5> in methanol (2.0 mL) and tetrahydrofuran (1.0 mL), a solution of 28% sodium methoxide in methanol (57.7 mg) was added and the resultant reaction mixture was stirred for 1 hour. To the reaction solution, 1M

264

hydrochloric acid was added and the mixture was extracted with ethyl acetate. The obtained organic phase was washed with brine and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was triturated with a mixed solution of n-hexane:ethyl acetate=2:1 to give the title compound (93 mg) as a white solid. The title compound is a racemic mixture.

Example 23

Synthesis of 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of 4-(5-bromo-6-methylpyridin-2-yloxy)-2-methylbutan-2-ol

To a suspension of sodium hydride (containing about 40% of a mineral oil, 0.38 g) in N,N-dimethylformamide (10 mL), 5-bromo-2-hydroxy-6-methylpyridine (1.00 g) and 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate (1.51 g) were added under ice-cooling and the resultant reaction mixture was stirred at 60° C. for 2.5 hours. To the mixture, 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate (0.50 g) was further added and the resultant reaction mixture was stirred at 60° C. for 1.5 hours. Sodium hydride (containing about 40% of a mineral oil, 40 mg) was further added. To the reaction mixture, a saturated aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=50:50 to 33:67) to give the title compound (1.3 g) as a pale yellow oil.

<Step 2> Synthesis of 4-[5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-methylpyridin-2-yl]oxy-2-methylbutan-2-ol

To a solution of the compound (2.85 g) obtained in (Example 23) <Step 1> and bis(neopentyl glycolate)diboron (2.82 g) in 1,4-dioxane (45 mL), potassium acetate (3.06 g) and a [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II)-dichloromethane adduct (0.42 g) were added. The mixture was degassed and then heated and refluxed for 16 hours. To the reaction mixture, water (200 mL) was added and the mixture was extracted with ethyl acetate (200 mL). The organic phase was washed with brine (80 mL) and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=95:5 to 80:20) to give the title compound (2.2 g).

<Step 3> Synthesis of 4-(((1R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)phenyl)boronic acid N-methyliminodiacetic acid ester

To a mixed solution of the compound (0.20 g) obtained in (Reference Example 1), (1S)-4-bromo-2,3-dihydro-1H-inden-1-ol (153 mg) that was commercially available or could be obtained by a known method, and tri-n-butylphosphine (0.50 mL) in tetrahydrofuran (3 mL), 1,1'-azobis(N,N-dimethylformamide) (0.35 g) was added under ice-cooling. The resultant reaction mixture was stirred at room temperature for

265

1.5 hours. From the reaction mixture, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=50:50 to 0:100). From the eluted solution, the solvent was distilled off under reduced pressure to give a crude product containing the title compound.

<Step 4> Synthesis of 5-(4-(((1R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)phenyl)isothiazol-3-ol 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (24.6 mg) was obtained from the crude product (178 mg) obtained in (Example 23) <Step 3>.

<Step 5> Synthesis of 3-hydroxy-5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazole 1-oxide (A)

A mixed solvent of the compound (50 mg) obtained in (Example 23) <Step 4>, the compound (49.4 mg) obtained in (Example 23) <Step 2>, bis(dibenzylideneacetone)palladium (7.1 mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos: 11.8 mg), potassium carbonate (34.2 mg), 1,4-dioxane (1.0 mL), and water (0.5 mL) was heated and refluxed for 4 hours. The reaction solution was extracted with ethyl acetate and the organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; ethyl acetate:methanol=100:0 to 80:20). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (12 mg) as a colorless amorphous solid.

<Step 6> Synthesis of 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)

In accordance with the method in (Example 7) <Step 2>, the title compound was obtained from the compound (0.13 g) obtained in (Example 23) <Step 5> and then each diastereomer of the title compound was obtained.

Primary fraction (10.3 mg, white amorphous solid, retention time 5.85 minutes (LC/MS), diastereomer a: Example 23 (A)-a)

Secondary fraction (3.3 mg, white amorphous solid, retention time 5.77 minutes (LC/MS), diastereomer b: Example 23 (A)-b)

Example 24

Synthesis of 5-[4-[[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of 4-(4-bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol

A mixed solution of 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate (4.24 g) synthesized in accordance with the method described in [WO 2009/067613 pamphlet, Example 308], 4-bromo-3,5-dimethylphenol (3.0 g), and potassium carbonate (3.09 g) in N,N-dimethylformamide (15 mL) was stirred at 80° C. for 3 hours. To the reaction mixture, ethyl acetate (200 mL) and water (100 mL) were added and the

266

mixture was extracted with ethyl acetate. The organic phase was successively washed with water (50 mL) and brine (50 mL) and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=80:20 to 70:30). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (3.9 g).

<Step 2> Synthesis of 4-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,5-dimethylphenoxy)-2-methylbutan-2-ol

In accordance with the method in (Example 23) <Step 2>, the title compound (2.65 g) was obtained using the compound (3.90 g) obtained in (Example 24) <Step 1>.

<Step 3> Synthesis of 5-[4-[[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]isothiazol-3-ol 1-oxide (A)

In accordance with the method in (Example 23) <Step 5>, the title compound (8 mg) was obtained as a pale yellow solid using the compound (50 mg) obtained in (Example 23) <Step 4> and the compound (0.12 g) obtained in (Example 24) <Step 2>.

<Step 4> Synthesis of 5-[4-[[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl]-2,3-dihydro-1H-inden-1-yl]oxy]phenyl]-1-oxo-1,2-thiazolidin-3-one (A)

In accordance with the method in (Example 7) <Step 2>, the title compound was obtained from the compound (0.17 g) obtained in (Example 24) <Step 3> and then each diastereomer of the title compound was obtained.

Primary fraction (34.3 mg, white amorphous solid, retention time 6.17 minutes (LC/MS), diastereomer a: Example 24 (A)-a)

Secondary fraction (40.5 mg, white amorphous solid, retention time 6.08 minutes (LC/MS), diastereomer b: Example 24 (A)-b)

Example 25

Synthesis of 4-(((1R)-1-(4-(1-oxo-1,2-thiazolidin-3-on-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A)

<Step 1> Synthesis of 2-(((S)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)tetrahydro-2H-pyran

In methylene chloride (16.2 mL), 3,4-dihydro-2H-pyran (10.6 mL) was dissolved. To the solution, a solution of 4M hydrogen chloride in 1,4-dioxane (31.1 μ L) was added and (1S)-4-bromo-2,3-dihydro-1H-inden-1-ol (10.0 g) that was commercially available or could be obtained by a known method was added. The resultant reaction mixture was stirred at room temperature for 3 hours. To the reaction mixture, a saturated aqueous sodium hydrogen carbonate solution (60 mL) was added and extracted with methylene chloride (60 mL). The organic phase was washed with brine (60 mL) and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chroma-

267

tography (eluent; n-hexane:ethyl acetate=95:5). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (15 g).

<Step 2> Synthesis of 5,5-dimethyl-2-((1S)-1-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-4-yl)-1,3,2-dioxaborinane

To a solution of the compound (14.0 g) obtained in (Example 25) <Step 1> in 1,4-dioxane (213 mL), 5,5,5',5'-tetramethyl-2,2'-di(1,3,2-dioxaborinane) (17.3 g), potassium acetate (18.8 g), and a 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride-dichloromethane complex (2.61 g) were sequentially added and the resultant reaction mixture was heated and refluxed for 3 hours. To the reaction mixture, water (300 mL) was added and the mixture was filtered with Celite while washing the mixture with ethyl acetate (250 mL). To the filtrate, brine (200 mL) was added and the mixture was extracted with ethyl acetate (200 mL). The organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=70:30). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (15.3 g) as an orange oil.

<Step 3> Synthesis of ((1S)-1-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1H-inden-4-yl)boronic acid

To a solution of the compound (8.20 g) obtained in (Example 25) <Step 2> in ethyl acetate (370 mL), water (1.10 L) was added and the resultant reaction mixture was stirred at room temperature for 16 hours. Liquid separation of the reaction mixture was conducted and the organic phase was washed with brine (200 mL) and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=90:10 to 50:50). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (3.00 g) as a yellowish white solid.

<Step 4> Synthesis of 4-(((1S)-1-((tetrahydro-2H-pyran-2-yl)oxy)-2,3-dihydro-1,4-inden-4-yl)oxy)benzonitrile

To a solution of the compound (0.50 g) obtained in (Example 25) <Step 3> in methylene chloride (16 mL), 4-hydroxybenzonitrile (0.19 g), copper(II) acetate (0.32 g), and triethylamine (1.16 mL) were added and the resultant reaction mixture was stirred in an oxygen atmosphere at room temperature for 3 days. The reaction mixture was filtered with Celite. From the filtrate, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography. From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (0.42 g) as a colorless oil.

<Step 5> Synthesis of (S)-4-((1-hydroxy-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile

The compound (0.40 g) obtained in (Example 25) <Step 4> was dissolved in a 1:1 mixed solvent (8.0 mL) of methanol and tetrahydrofuran. To the solution, 1M hydrochloric acid (4.0 mL) was added and the resultant reaction mixture was stirred at room temperature for 18 hours. From the reaction

268

mixture, the solvent was distilled off under reduced pressure. To the residue, a 1M sodium hydroxide aqueous solution was added to make the mixture basic. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (0.29 g) as a colorless oil.

<Step 6> Synthesis of (R)-4-((4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenylboronic acid N-methyliminodiacetic acid ester

In accordance with the method in (Example 1) <Step 3>, a mixture (330 mg) containing the title compound was obtained as a white solid from the compound (0.3 g) obtained in (Example 25) <Step 5>.

<Step 7> Synthesis of 4-(((1R)-1-(4-(3-hydroxy-1-oxidoisothiazol-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (92 mg) was obtained as a pale yellow solid from the compound (0.2 g) obtained in (Example 25) <Step 6>.

<Step 8> Synthesis of 4-(((1R)-1-(4-(1-oxo-1,2-thiazolidin-3-on-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (A)

In accordance with the method in (Example 7) <Step 2>, the title compound was obtained from the compound (130 mg) obtained in (Example 25) <Step 7> and then each diastereomer of the title compound was obtained.

Primary fraction (25.3 mg, white solid, retention time 5.65 minutes (LC/MS), diastereomer a: Example 25 (A)-a)

Secondary fraction (31.4 mg, white solid, retention time 5.60 minutes (LC/MS), diastereomer b: Example 25 (A)-b)

Example 26

Synthesis of 4-(((1R)-1-(4-(1,1-dioxo-1,2,6-thiadiazinan-3-on-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile

<Step 1> Synthesis of ethyl 3-(4-hydroxyphenyl)-3-(2,2,2-trifluoroacetamide)propionate

To a solution of ethyl 3-amino-3-(4-hydroxyphenyl)propionate (1.0 g) that was commercially available or could be obtained by a known method in methylene chloride (0.41 mL), trifluoroacetic anhydride (0.70 mL) was added under 10° C. and the resultant reaction mixture was stirred at room temperature for 5 hours. To the reaction mixture, pyridine (0.41 mL) was added at 10° C. or lower and the resultant reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture, trifluoroacetic anhydride (0.70 mL) and pyridine (0.41 mL) were further added and the resultant reaction mixture was stirred at room temperature for 15 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was diluted with ethyl acetate (50 mL), then successively washed with 0.5M hydrochloric acid (50 mL) and water (50 mL), and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was washed with hexane to give the title compound (900 mg) as a yellow solid.

269

<Step 2> Synthesis of ethyl 3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-(2,2,2-trifluoroacetamide)propionate

In accordance with the method in (Example 23) <Step 3>, the title compound (680 mg) was obtained as a yellow oil using the compound (0.40 g) obtained in (Example 26) <Step 1> and the compound (0.33 g) obtained in (Example 25) <Step 5>.

<Step 3> Synthesis of ethyl 3-amino-3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)propionate

The compound (0.45 g) obtained in (Example 26) <Step 2> was dissolved in ethanol (10 mL). To the solution, sodium borohydride (63.2 mg) was added and the resultant reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL). The obtained organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=0:100). From the eluted solution, the solvent was distilled off under reduced pressure to give a mixture (290 mg) containing the title compound as a colorless solid.

<Step 4> Synthesis of ethyl

3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-(sulfamoylamino)propionate

To a solution of chlorosulfonyl isocyanate in tetrahydrofuran, aqueous tetrahydrofuran was added at 10° C. or lower. The reaction mixture was stirred at room temperature for 30 minutes to prepare a solution of sulfamoyl chloride in tetrahydrofuran.

A solution of the compound obtained in (Example 26) <Step 3> in tetrahydrofuran was prepared in another container. To the container, pyridine (0.10 ml) was added and the solution of sulfamoyl chloride in tetrahydrofuran was added dropwise under 10° C. The resultant reaction mixture was stirred at room temperature for 19 hours. To the reaction mixture, water (30 mL) was added. The mixture was extracted with ethyl acetate (20 mL) twice. The obtained organic phase was washed with water (20 mL) and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography. From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound.

<Step 5> Synthesis of 4-(((1R)-1-(4-(1,1-dioxo-1,2,6-thiadiazinan-3-on-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile

The compound (15 mg) obtained in (Example 26) <Step 4> was dissolved in ethanol (1.5 mL) and a 1M sodium hydroxide aqueous solution (0.15 mL) was added to the solution. The resultant reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution (1 mL) and water (1 mL) were added. The mixture was extracted with ethyl acetate (10 mL) and the organic phase was dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=0:

270

100). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (7.5 mg) as a colorless amorphous solid.

Each compound of (Example 27) to (Example 28) below was synthesized by the same method or a similar method in (Example 1) or (Example 26).

Example 27

5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one

Example 28

5-(4-((7-(trifluoromethyl)-2,3-dihydrobenzofuran-3-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one

Example 29

Synthesis of 5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)

To a solution of 1N L-Selectride in tetrahydrofuran (14.8 mL), tetrabutylammonium chloride (4.1 g) was added under ice-cooling and a solution of the compound (1 g) obtained in (Example 23) <Step 4> in anhydrous THF (5 mL) was added dropwise under 3° C. The reaction mixture was allowed to reach room temperature and stirred for 2 days. To the reaction mixture, 1M hydrochloric acid was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (0.44 g) as a yellow solid. The reduced title compound in this step is a mixture of diastereomers because the compound has a new asymmetric center (carbon atom).

Example 30

Synthesis of 5-(4-(((R)-4-(2,6-dimethyl 4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one (A)

<Step 1> Synthesis of 2-bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propoxy)benzene

In accordance with the method in (Example 23) <Step 1>, the title compound (289 g) was obtained as a white solid from 4-bromo-3,5-dimethylphenol (217 g) and 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (300 g).

<Step 2> Synthesis of 2-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane

In accordance with the method in (Example 23) <Step 2>, the title compound (0.70 g) was obtained as a beige solid from the compound (1.0 g) obtained in (Example 30) <Step 1>.

<Step 3> Synthesis of 5-(4-(((R)-4-(2,6-dimethyl 4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1-oxo-1,2-thiazolidin-3-one

To a solution of the compound (0.10 g) in (Example 29), the compound (0.13 g) obtained in (Example 30) <Step 2>,

271

potassium carbonate (34 mg), 2-dicyclohexylphosphino-2', 4',6'-triisopropylbiphenyl (XPhos: 23 mg), and bis(dibenzylideneacetone)palladium (14 mg) in 1,4-dioxane (4 mL), water (2 mL) was added. The inside of the reaction system was purged with nitrogen and the resultant reaction mixture was heated and refluxed for 2 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (55 mg) as a pale yellow solid. The title compound is a mixture of diastereomers because it has the asymmetric center as with the compound in Example 29.

Example 31

Synthesis of 5-[4-[[3-[2,6-dimethyl 4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

<Step 1> Synthesis of N,N-bis((2-(trimethylsilyl)ethoxy)methyl)methanesulfonamide

Sodium hydride (4.6 g) was added to DMF (35 ml). To the solution, a solution of methanesulfonamide (5.0 g) in DMF (15 ml) was added dropwise. (2-(chlorotrimethoxyethyl)trimethylsilane (18.6 ml) was added to the solution and the resultant reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (7.4 g) as a colorless oil.

<Step 2> Synthesis of 4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1',1'-biphenyl]-3-yl)methoxy)benzaldehyde

To a solution of the compound (3.0 g) in (Reference Example 2) in DMF (40 ml), potassium carbonate (1.2 g) and 4-hydroxybenzaldehyde (0.94 g) were added at room temperature. The inside of the reaction system was purged with nitrogen and the mixture was heated and stirred at 80° C. for 2 hours. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (3.3 g) as a pale yellow oil.

<Step 3> Synthesis of (E)-2-(4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1',1'-biphenyl]-3-yl)methoxy)phenyl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)ethanesulfonamide

A solution of the compound (2.4 g) in (Example 31) <Step 1> in THF (7 ml) was cooled in an acetonitrile-dry ice bath. To the solution, a solution of 1M lithium hexamethyldisilazane in THF (14.6 ml) was added dropwise and the resultant reaction mixture was stirred at the same temperature for 50 minutes. Next, diethyl chlorophosphonate (1.1 ml) was added

272

dropwise and the resultant reaction mixture was further stirred for 90 minutes. Then, a solution of the compound (3.0 g) in (Example 31) <Step 2> in THF (10 ml) was added dropwise. The resultant reaction mixture was stirred at the same temperature for 30 minutes, next stirred under ice-cooling for 1 hour, then allowed to reach room temperature, and stirred for 1 hour. To the reaction mixture, 1M hydrochloric acid was added. The mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, then washed with a half saturated salt solution, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (6.0 g) as a pale yellow oil.

<Step 4> Synthesis of dimethyl 2-(2-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-1-(4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1',1'-biphenyl]-3-yl)methoxy)phenyl)ethyl)malonate

To a solution of dimethyl malonate (1.5 ml) in THF (10 ml), a solution of 28% sodium methoxide in methanol (2.6 g) was added at room temperature. The mixture was stirred for 10 minutes. To the reaction mixture, a solution of the compound (3.5 g) in (Example 31) <Step 3> in THF (30 ml) was added and the resultant reaction mixture was heated and refluxed for 65 hours. To the reaction mixture, a saturated aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (3.5 g) as a colorless oil.

<Step 5> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1',1'-biphenyl]-3-yl)methoxy)phenyl)butanoate

To a solution of the compound (3.5 g) in (Example 31) <Step 4> in DMF (35 ml), sodium chloride (0.22 g) and water (0.14 ml) were added and the resultant reaction mixture was heated and refluxed for 17 hours. To the reaction mixture, water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (3.0 g) as a colorless oil.

<Step 6> Synthesis of methyl 3-(4-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1',1'-biphenyl]-3-yl)methoxy)phenyl)-4-sulfamoylbutanoate

To a solution of the compound (1.5 g) in (Example 31) <Step 5> in acetic acid (15 ml), water (7.5 ml) was added and the resultant reaction mixture was heated and stirred at 80° C. for 3 hours. To the reaction mixture, water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chroma-

273

tography (eluent; n-hexane:ethyl acetate) to give the title compound (0.34 g) as a colorless oil.

<Step 7> Synthesis of 5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

To a solution of the compound (20 mg) in (Example 31) <Step 6> in methanol (0.40 ml), a solution of 28% sodium methoxide in methanol (8.3 mg) was added at room temperature and the resultant reaction mixture was stirred for 1 hour. To the reaction mixture, 1M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (15 mg) as a colorless solid.

Example 32

Synthesis of 4-(((1R)-1-(4-(1,1-dioxo-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile

<Step 1> Synthesis of (E)-2-(4-(benzyloxy)phenyl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)ethanesulfonamide

In accordance with the method in (Example 31) <Step 3>, the title compound (6.1 g) was obtained as a colorless solid from the compound (7.5 g) obtained in (Example 31) <Step 1> and 4-benzyloxybenzaldehyde (4.5 g).

<Step 2> Synthesis of dimethyl 2-(1-(4-(benzyloxy)phenyl)-2-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)ethyl)malonate

In accordance with the method in (Example 31) <Step 4>, the title compound (2.5 g) was obtained as a colorless oil from the compound (3.0 g) obtained in (Example 32) <Step 1>.

<Step 3> Synthesis of methyl 3-(4-(benzyloxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoate

In accordance with the method in (Example 31) <Step 5>, the title compound (1.3 g) was obtained as a colorless oil from the compound (2.4 g) obtained in (Example 32) <Step 2>.

<Step 4> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(hydroxyphenyl)butanoate

To a solution of the compound (20 mg) in (Example 32) <Step 3> in methanol (1.0 ml), 10% palladium-carbon (2.0 mg) was added and the resultant reaction mixture was stirred in a hydrogen atmosphere for 16 hours. The inside of the reaction system was purged with nitrogen. Then, the reaction mixture was filtered with Celite. From the filtrate, the solvent was distilled off under reduced pressure to give the title compound (17 mg).

<Step 5> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate

A mixture of the compound (0.23 g) in (Example 25) <Step 5>, the compound (0.48 g) in (Example 32) <Step 4>,

274

molecular sieves 3A (0.50 g), and toluene (9.0 ml) was heated and refluxed. To the mixture, cyanomethylenetriethylphosphorane (1.2 ml) was added dropwise and the resultant reaction mixture was heated and refluxed for 2.5 hours. After the reaction mixture was allowed to cool to room temperature, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound (0.25 g) as a pale yellow viscous oil.

<Step 6> Synthesis of 4-(((1R)-1-(4-(1,1-dioxo-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile

To a solution of the compound (30 mg) in (Example 32) <Step 5> in THF (0.6 ml), a solution of 1M tetrabutylammonium fluoride in THF (0.15 ml) was added at room temperature. The resultant reaction mixture was stirred at room temperature for 30 minutes, then heated and refluxed for 1 hour, and stirred at room temperature for 16 hours. The reaction mixture was filtered and washed with ethyl acetate. To the obtained organic phase, 1M hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol) to give the title compound (3.2 mg) as a pale brown solid.

Example 33

Synthesis of 5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one

<Step 1> Synthesis of (R)-4-((4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)benzaldehyde

In accordance with the method in (Example 1) <Step 3>, the title compound (5.5 g) was obtained as a colorless solid from (S)-4-bromo-2,3-dihydro-1H-inden-1-ol (6.0 g) and 4-hydroxybenzaldehyde (3.5 g).

<Step 2> Synthesis of (R,E)-2-(4-((4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)ethanesulfonamide

In accordance with the method in (Example 31) <Step 3>, the title compound (8.2 g) was obtained as a yellow oil from the compound (6.0 g) obtained in (Example 31) <Step 1> and the compound (5.4 g) obtained in (Example 33) <Step 1>.

<Step 3> Dimethyl 2-(2-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-1-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)ethyl)malonate

In accordance with the method in (Example 31) <Step 4>, the title compound (9.6 g) was obtained as a yellow oil from the compound (8.2 g) obtained in (Example 33) <Step 2>.

<Step 4> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate

In accordance with the method in (Example 31) <Step 5>, the title compound (5.9 g) was obtained as a colorless oil from the compound (9.6 g) obtained in (Example 33) <Step 3>.

275

<Step 5> Synthesis of 5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one

In accordance with the method in (Example 32) <Step 6>, the title compound (5.1 mg) was obtained as a pale brown solid from the compound (30 mg) obtained in (Example 33) <Step 4>.

Example 34

Synthesis of 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one

In accordance with the method in (Example 30) <Step 3>, the title compound (6.0 mg) was obtained as a white solid from the compound (17 mg) obtained in (Example 33) and the compound (16 mg) obtained in (Example 24) <Step 2>.

Example 35

Synthesis of 5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

<Step 1> Synthesis of (E)-2-(4-((3-bromobenzyl)oxy)phenyl)-N,N-bis((2-(trimethylsilyl)ethoxy)methyl)ethanesulfonamide

In accordance with the method in (Example 31) <Step 3>, the title compound (18 g) was obtained as a white solid from 4-[(3-bromobenzyl)oxy]benzaldehyde (11 g) and the compound (13.4 g) obtained in (Example 31) <Step 1>.

<Step 2> Synthesis of dimethyl 2-(2-(N,N-bis((2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-1-(4-((3-bromobenzyl)oxy)phenyl)ethyl)malonate

In accordance with the method in (Example 31) <Step 4>, the title compound (23 g) was obtained as a colorless oil from the compound (18 g) obtained in (Example 35) <Step 1>.

<Step 3> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((3-bromobenzyl)oxy)phenyl)butanoate

In accordance with the method in (Example 31) <Step 5>, the title compound (21 g) was obtained as a colorless oil from the compound (23 g) obtained in (Example 35) <Step 2>.

<Step 4> Synthesis of methyl 3-(4-((3-bromobenzyl)oxy)phenyl)-4-sulfamoylbutanoate

In accordance with the method in (Example 31) <Step 6>, the title compound (0.32 g) was obtained as a colorless oil from the compound (1.0 g) obtained in (Example 35) <Step 3>.

<Step 5> Synthesis of 5-(4-((3-bromobenzyl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 31) <Step 7>, the title compound (0.12 g) was obtained as a white solid from the compound (0.16 g) obtained in (Example 35) <Step 4>.

276

<Step 6> Synthesis of 5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one

In accordance with the method in (Example 30) <Step 3>, the title compound (29 mg) was obtained as a white solid from the compound (0.10 g) obtained in (Example 35) <Step 5> and 4-((5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4,6-dimethylpyridin-2-yl)oxy)-2-methylbutan-2-ol (86 mg) synthesized by a similar method of (Example 23) <Step 2>.

Example 36

Synthesis of 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 23) <Step 5>, the title compound (5.0 mg) was obtained as a white solid from the compound (40 mg) obtained in (Example 33) and the compound (31 mg) obtained in (Example 23) <Step 2>.

Example 37

Synthesis of 5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

<Step 1> Synthesis of methyl 3-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoate

In accordance with the method in (Example 23) <Step 5>, the title compound (100 mg) was obtained as a colorless amorphous from the compound (40 mg) obtained in (Example 33) <Step 4> and (2,6-dimethylphenyl)boronic acid (28 mg).

<Step 2> Synthesis of 3-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoic acid

To a mixed solution of the compound (70 mg) obtained in (Example 37) <Step 1> in methanol (1.0 mL) and tetrahydrofuran (1.0 mL), a 1M sodium hydroxide aqueous solution (0.14 mL) was added and the resultant reaction mixture was stirred at 65° C. for 1 hour. To the reaction mixture, 1M hydrochloric acid was added and the resultant reaction mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (58 mg) as a pale yellow amorphous.

<Step 3> Synthesis of 3-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid

In accordance with the method in (Example 32) <Step 6>, the title compound (23 mg) was obtained as a pale yellow amorphous from the compound (50 mg) obtained in (Example 37) <Step 2>.

277

<Step 4> Synthesis of 5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 14) <Step 6>, the title compound (11 mg) was obtained as a colorless amorphous from the compound (20 mg) obtained in (Example 37) <Step 3>.

Example 38

Synthesis of 5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

<Step 1> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate

In accordance with the method in (Example 23) <Step 5>, the title compound (0.24 g) was obtained as a colorless oil from the compound (0.30 g) obtained in (Example 33) <Step 4>.

<Step 2> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid

In accordance with the method in (Example 37) <Step 2>, the title compound (0.19 g) was obtained as a colorless oil from the compound (0.22 g) obtained in (Example 38) <Step 1>.

<Step 3> Synthesis of 4-sulfamoyl-3-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid

In accordance with the method in (Example 32) <Step 6>, the title compound (0.10 g) was obtained as a pale yellow amorphous from the compound (0.19 g) obtained in (Example 38) <Step 2>.

<Step 4> Synthesis of 5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 14) <Step 6>, the title compound (73 mg) was obtained as a colorless amorphous from the compound (90 mg) obtained in (Example 38) <Step 3>.

Example 39

Synthesis of 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

<Step 1> Synthesis of methyl

4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate

278

In accordance with the method in (Example 23) <Step 5>, the title compound (0.28 g) was obtained as a colorless amorphous from the compound (0.30 g) obtained in (Example 33) <Step 4>.

<Step 2> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid

In accordance with the method in (Example 37) <Step 2>, the title compound (0.25 g) was obtained as a brown amorphous from the compound (0.25 g) obtained in (Example 39) <Step 1>.

<Step 3> Synthesis of 3-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid

In accordance with the method in (Example 32) <Step 6>, the title compound (48 mg) was obtained as a pale brown amorphous from the compound (0.22 g) obtained in (Example 39) <Step 2>.

<Step 4> Synthesis of 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 14) <Step 6>, the title compound (36 mg) was obtained as a pale brown amorphous from the compound (40 mg) obtained in (Example 39) <Step 3>.

Example 40

5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

<Step 1> Optical Resolution of methyl 3-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)sulfamoyl)butanoate

Optical resolution of the compound obtained in (Example 33) <Step 4> was performed by preparative chromatography (column: CHIRALPAK AS-H (250 mm×4.6 mm) manufactured by Daicel Chemical Industries, Ltd., eluent; carbon dioxide:2-propanol (containing 0.05% diethylamine)=95:5 to 60:40 (V/V), flow rate: 2.5 mL/minute, detection: UV 220 nm) to give each enantiomer of the title compound.

Primary fraction (7.1 g, white solid, >99% ee, retention time 5.2 minutes (enantiomer A: Example 1-5 (C)))

Secondary fraction (8.9 g, white solid, >98% ee, retention time 5.6 minutes (enantiomer B: Example 1-5 (D)))

Hereinafter, the compounds and derivatives of them synthesized using the enantiomer C (Example 40-1 (C)) obtained in (Example 40) <Step 1> are expressed as "name of the compound+(C)" and the compounds and derivatives of them synthesized using the enantiomer D (Example 40-1 (D)) obtained in (Example 40) <Step 1> are expressed as "name of the compound+(D)".

279

<Step 2> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate (C)

In accordance with the method in (Example 23) <Step 5>, the title compound (1.6 g) was obtained as a colorless oil from the enantiomer C (Example 40-1 (C)) (1.6 g) obtained in (Example 40) <Step 1>.

<Step 3> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid (C)

In accordance with the method in (Example 37) <Step 2>, the title compound (1.4 g) was obtained as a pale yellow amorphous from the compound (1.5 g) obtained in (Example 40) <Step 2>.

<Step 4> Synthesis of 3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid (C)

In accordance with the method in (Example 32) <Step 6>, the title compound (0.4 g) was obtained as a colorless oil from the compound (1.3 g) obtained in (Example 40) <Step 3>.

<Step 5> Synthesis of 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

In accordance with the method in (Example 14) <Step 6>, the title compound (0.18 g) was obtained as a colorless amorphous from the compound (0.20 g) obtained in (Example 40) <Step 4>.

Example 41

Synthesis of 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (D)

<Step 1> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate (D)

In accordance with the method in (Example 23) <Step 5>, the title compound (1.6 g) was obtained as a colorless oil from the enantiomer D (Example 40-1 (D)) (1.6 g) obtained in (Example 40) <Step 1>.

<Step 2> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid (D)

In accordance with the method in (Example 37) <Step 2>, the title compound (1.7 g) was obtained as a colorless oil from the compound (1.6 g) obtained in (Example 41) <Step 1>.

280

<Step 3> Synthesis of 3-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid (D)

In accordance with the method in (Example 32) <Step 6>, the title compound (0.52 g) was obtained as a white solid from the compound (1.7 g) obtained in (Example 41) <Step 2>.

<Step 4> Synthesis of 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1,4-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (D)

In accordance with the method in (Example 14) <Step 6>, the title compound (22 mg) was obtained as a white solid from the compound (0.39 g) obtained in (Example 41) <Step 3>.

The compounds of Example 42 to Example 46 below were synthesized by the same method as or a similar method to the method in Example 41 by performing Step 1 to Step 4 using the compound of the enantiomer C (Example 40-1 (C)) obtained in (Example 40) <Step 1> and a corresponding substituted boronic acid ester or boronic acid.

Example 42

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

Example 43

5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

Example 44

5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

Example 45

5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

Example 46

5-(4-(((R)-4-(4-methoxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

Example 47

Synthesis of 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-1,2-thiazinan-3-one 1,1-dioxide

<Step 1> Synthesis of (R)-4-((4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylbenzaldehyde

In accordance with the method in (Example 23) <Step 3>, the title compound (1.5 g) was obtained as a beige solid from (1S)-4-bromo-2,3-dihydro-1H-inden-1-ol (1.6 g) that was

281

commercially available or could be obtained by a known method and commercially available 4-hydroxy-2-methylbenzaldehyde (1.0 g).

<Step 2> Synthesis of (R)-(E)-2-(4-((4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-N,N-bis(2-(trimethylsilyl)ethoxymethyl)ethanesulfonamide

In accordance with the method in (Example 31) <Step 3>, the title compound (1.8 g) was obtained as a yellow oil from the compound (1.6 g) obtained in (Example 31) <Step 1> and the compound (1.5 g) obtained in (Example 47) <Step 1>.

<Step 3> Synthesis of dimethyl 2-(1-(4-((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-2-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)ethyl)malonate

In accordance with the method in (Example 31) <Step 4>, the title compound (1.4 g) was obtained as a colorless oil from the compound (1.8 g) obtained in (Example 47) <Step 2>.

<Step 4> Synthesis of methyl 3-(4-((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoate

In accordance with the method in (Example 31) <Step 5>, the title compound (0.44 g) was obtained as a colorless oil from the compound (1.3 g) obtained in (Example 47) <Step 3>.

<Step 5> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)butanoate

In accordance with the method in (Example 23) <Step 5>, the title compound (0.31 g) was obtained as a colorless oil from the compound (0.40 g) obtained in (Example 47) <Step 4> and the compound (0.19 g) obtained in (Example 24) <Step 2>.

<Step 6> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)butanoic acid

In accordance with the method in (Example 37) <Step 2>, the title compound (0.24 g) was obtained as a pale yellow amorphous from the compound (0.30 g) obtained in (Example 47) <Step 5>.

<Step 7> Synthesis of 3-(4-((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-4-sulfamoylbutanoic acid

In accordance with the method in (Example 32) <Step 6>, the title compound (65 mg) was obtained as a pale yellow amorphous from the compound (0.20 g) obtained in (Example 47) <Step 6>.

282

<Step 8> Synthesis of 5-(4-((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 14) <Step 6>, the title compound (50 mg) was obtained as a pale yellow amorphous from the compound (60 mg) obtained in (Example 47) <Step 7>.

Example 48

Synthesis of 5-(4-((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

<Step 1> Synthesis of methyl 3-(4-((R)-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoate

In accordance with the method in (Example 23) <Step 1>, the title compound (5.0 g) was obtained as a yellow oil from the compound (5.0 g) obtained in (Example 33) <Step 4>.

<Step 2> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((R)-4-hydroxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate

Under ice-cooling, to a mixed solution of acetone (10 mL) and water (30 mL), sodium hydrogen carbonate (2.2 g) was added and thereto, OXONE (2.0 g) was slowly added. To the resultant reaction mixture, further acetone (80 mL) was added and thereto, a solution of the compound (1.0 g) obtained in (Example 48) <Step 1> in acetone (10 mL) was added, followed by stirring the resultant reaction mixture for 1 hour. To the reaction mixture, a 10% sodium hydrogen sulfite aqueous solution was added and 1M hydrochloric acid was added. The reaction mixture was extracted with ethyl acetate. The organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure to give the title compound (0.80 g).

<Step 3> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((R)-4-phenoxy-2,3-dihydro-1'-1-inden-1-yl)oxy)phenyl)butanoate

In accordance with the method in (Example 25) <Step 4>, the title compound (0.75 g) was obtained as a colorless oil from the compound (0.80 g) obtained in (Example 48) <Step 2>.

<Step 4> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid

In accordance with the method in (Example 37) <Step 2>, the title compound (0.71 g) was obtained as a colorless oil from the compound (0.80 g) obtained in (Example 48) <Step 3>.

283

<Step 5> Synthesis of 3-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid

In accordance with the method in (Example 32) <Step 6>, the title compound (0.19 g) was obtained as a white solid from the compound (0.71 g) obtained in (Example 48) <Step 4>.

<Step 6> Synthesis of 5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide

In accordance with the method in (Example 14) <Step 6>, the title compound (24 mg) was obtained as a white solid from the compound (0.11 g) obtained in (Example 48) <Step 5>.

Example 49

Synthesis of 5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

<Step 1> Synthesis of methyl 3-(4-(((R)-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoate (C)

In accordance with the method in (Example 23) <Step 1>, the title compound (2.2 g) was obtained as a colorless oil from the enantiomer C (Example 40-1 (C)) (2.5 g) obtained in (Example 40) <Step 1>.

<Step 2> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-hydroxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate (C)

In accordance with the method in (Example 48) <Step 2>, the title compound (2.0 g) was obtained as a colorless oil from the compound (1.2 g) obtained in (Example 49) <Step 1>.

<Step 3> Synthesis of methyl 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoate (C)

In accordance with the method in (Example 25) <Step 4>, the title compound (0.95 g) was obtained as a colorless oil from the compound (0.98 g) obtained in (Example 49) <Step 2>.

<Step 4> Synthesis of 4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)-3-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)butanoic acid (C)

In accordance with the method in (Example 37) <Step 2>, the title compound (0.92 g) was obtained as a white solid from the compound (0.95 g) obtained in (Example 49) <Step 3>.

<Step 5> Synthesis of 3-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid (C)

In accordance with the method in (Example 32) <Step 6>, the title compound (0.17 g) was obtained as a white solid from the compound (0.92 g) obtained in (Example 49) <Step 4>.

284

<Step 6> Synthesis of 5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide (C)

In accordance with the method in (Example 14) <Step 6>, the title compound (67 mg) was obtained as a white solid from the compound (0.17 g) obtained in (Example 49) <Step 5>.

Example 50

Synthesis of 4-(((1R)-1-(4-(1,1-dioxide-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (C)

<Step 1> Synthesis of methyl 3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(tri methylsilyl)ethoxymethyl)sulfamoyl)butanoate (C)

In accordance with the method in (Example 25) <Step 4>, the title compound (0.55 g) was obtained as a colorless oil from the compound (0.98 g) obtained in (Example 49) <Step 2>.

<Step 2> Synthesis of 3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-(N,N-bis(2-(trimethylsilyl)ethoxymethyl)sulfamoyl)butanoic acid (C)

In accordance with the method in (Example 37) <Step 2>, the title compound (0.51 g) was obtained as a white solid from the compound (0.55 g) obtained in (Example 50) <Step 1>.

<Step 3> Synthesis of 3-(4-(((R)-4-(4-cyanophenoxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4-sulfamoyl butanoic acid (C)

In accordance with the method in (Example 32) <Step 6>, the title compound (0.18 g) was obtained as a white solid from the compound (0.51 g) obtained in (Example 50) <Step 2>.

<Step 4> Synthesis of 4-(((1R)-1-(4-(1,1-dioxide-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile (C)

In accordance with the method in (Example 14) <Step 6>, the title compound (0.12 g) was obtained as a white solid from the compound (0.18 g) obtained in (Example 50) <Step 3>.

Example 51

Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

<Step 1> Synthesis of (S)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-ol

(1S)-4-hydroxy-2,3-dihydro-1H-inden-1-ol (1.0 g) that was commercially available or could be obtained by a known method and the compound (2.5 g) obtained in (Example 23) <Step 2> were dissolved in methylene chloride (50.0 mL) and to the resultant reaction solution, molecular sieves 4A (powder; 2.0 g), copper(II) acetate (1.5 g), and triethylamine (4.6 mL) were added. The resultant reaction mixture was stirred in

285

an oxygen atmosphere at room temperature for 18 hours. To the reaction mixture, silica gel (20 g) was added and the reaction mixture was filtered with Celite. The filtrate was washed with ethyl acetate and from the filtrate, the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=100:0 to 55:45) and was further purified by silica gel column chromatography (NH silica, eluent; n-hexane:ethyl acetate=100:0 to 55:45). From the eluted solution, the solvent was distilled off under reduced pressure to give the title compound (1.0 g) as a pale yellow oil.

<Step 2> Synthesis of (R)-2-(4-((4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

In accordance with the method in (Example 1) <Step 3>, the title compound (0.68 g) was obtained as a pale orange amorphous from the compound (1.0 g) obtained in (Example 51) <Step 1> and the compound (0.73) obtained in (Reference Example 1).

<Step 3> Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazole 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (0.12 g) was obtained as a pale yellow solid using the enantiomer A (Example 1-5 (A)) (79 mg) obtained in (Example 1) <Step 5> from the compound (0.20 g) obtained in (Example 51) <Step 2>.

<Step 4> Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

To a solution of 1N L-Selectride in tetrahydrofuran (1.1 mL), tetrabutylammonium chloride (0.31 g) was added under ice-cooling and thereto, a solution of the compound (0.1 g) obtained in (Example 51) <Step 3> in anhydrous THF (0.35 mL) was added dropwise at or below 3° C. The reaction mixture was allowed to reach room temperature and stirred for 1 day. To the reaction mixture, 1M hydrochloric acid was added. The mixture was extracted with ethyl acetate. The organic phase was washed with brine and then dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound. Optical resolution of the solid of the title compound was performed by preparative chromatography (column: CHIRALPAK OJ-H (2 cm×25 cm) manufactured by Daicel Chemical Industries, Ltd., eluent; ethanol:trifluoroacetic acid=100:0.1 (V/V), flow rate: 2 mL/minute) to give each diastereomer of the title compound. The retention time was determined by LC/MS.

Primary fraction (27 mg, retention time 5.87 minutes, diastereomer a: Example 51 (A)-a)

Secondary fraction (21 mg, retention time 5.82 minutes, diastereomer b: Example 51 (A)-b)

286

Example 52

Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

<Step 1> Synthesis of (S)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-ol

A mixed solution of (1S)-4-hydroxy-2,3-dihydro-1H-inden-1-ol (0.5 g) that was commercially available or could be obtained by a known method, 2,2,6,6-tetramethyl-3,5-heptanedione (0.55 mL), copper (I) iodide (0.16 g), cesium carbonate (2.7 g), 5-bromo-2-methoxypyridine (0.48 mL), and N-methylpyrrolidone (6.5 mL) was heated and stirred by a microwave at 100° C. for 45 minutes. The reaction mixture was allowed to reach room temperature, was filtered with Celite, and was washed with ethyl acetate. To the reaction mixture, a saturated aqueous ammonium chloride solution was added and the resultant reaction mixture was extracted with ethyl acetate. The resultant extract was washed with brine and then dried over anhydrous sodium sulfate. From the resultant extract, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate=9:1 to 3:1), followed by distillation-off of the solvent under reduced pressure to give the title compound (0.42 g) as a brown oil.

<Step 2> Synthesis of (R)-2-(4-((4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

In accordance with the method in (Example 1) <Step 3>, the title compound (0.26 g) was obtained as a pale yellow amorphous from the compound (0.20 g) obtained in (Example 52) <Step 1> and the compound (0.23 g) obtained in (Reference Example 1).

<Step 3> Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazole 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (0.10 g) was obtained as a white solid using the enantiomer A (Example 1-5 (A)) (0.12 g) obtained in (Example 1) <Step 5> from the compound (0.25 g) obtained in (Example 52) <Step 2>.

<Step 4> Synthesis of 3-hydroxy-5-(4-(((R)-4-((6-methoxypyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

In accordance with the method in (Example 51) <Step 4>, the title compound was obtained from the compound (0.30 g) obtained in (Example 52) <Step 3> and by the following preparative chromatography, each diastereomer (primary fraction (diastereomer-a): 54 mg, secondary fraction (diastereomer-b): 24 mg) thereof was obtained.

Example 53

Synthesis of 3-hydroxy-5-(4-(((R)-4-(m-tolyloxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

<Step 1> Synthesis of (S)-4-(m-tolyloxy)-2,3-dihydro-1H-inden-1-ol

In accordance with the method in (Example 51) <Step 1>, the title compound (0.61 g) was obtained as a pale yellow

287

solid from (1S)-4-hydroxy-2,3-dihydro-1H-inden-1-ol (1.0 g) that was commercially available and could be obtained by a known method and m-tolylboronic acid (1.1 g).

<Step 2> Synthesis of ((R)-6-methyl-2-(4-((4-(m-tolylloxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,3,6,2-dioxazaborocane-4,8-dione

In accordance with the method in (Example 1) <Step 3>, the title compound (0.75 g) was obtained as a beige amorphous from the compound (0.60 g) obtained in (Example 53) <Step 1> and the compound (0.61 g) obtained in (Reference Example 1).

<Step 3> Synthesis of 3-hydroxy-5-(4-(((R)-4-(m-tolylloxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazole 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (0.16 g) was obtained as a pale yellow solid using the enantiomer A (Example 1-5 (A)) (0.14 g) obtained in (Example 1) <Step 5> from the compound (0.30 g) obtained in (Example 53) <Step 2>.

<Step 4> Synthesis of 3-hydroxy-5-(4-(((R)-4-(m-tolylloxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

In accordance with the method in (Example 51) <Step 4>, the title compound was obtained from the compound (0.26 g) obtained in (Example 53) <Step 3> and by the following preparative chromatography, each diastereomer (primary fraction (diastereomer-a): 45 mg, secondary fraction (diastereomer-b): 44 mg) thereof was obtained.

Example 54

Synthesis of 5-(4-(((R)-4-(6-(2-ethoxyethoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)

<Step 1> Synthesis of 3-bromo-6-(2-ethoxyethoxy)-2-methylpyridin

In accordance with the method in (Example 23) <Step 1>, the title compound (3.3 g) was obtained using 5-bromo-6-methylpyridine-2-ol (3.0 g) from 1-chloro-2-ethoxyethane (1.9 mL).

<Step 2> Synthesis of 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-(2-ethoxyethoxy)-2-methylpyridine

In accordance with the method in (Example 23) <Step 2>, the title compound (3.1 g) was obtained as an oil from the compound (5.0 g) obtained in (Example 54) <Step 1>.

<Step 3> Synthesis of 5-(4-(((R)-4-(6-(2-ethoxyethoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)

To a solution of the compound (0.15 g) in (Example 29), the compound (0.16 g) obtained in (Example 54) <Step 2>, potassium carbonate (0.10 g), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos: 35 mg), and bis(dibenzylideneacetone)palladium (21 mg) in 1,4-dioxane (6 mL),

288

water (3 mL) was added. The inside of the reaction system was purged with nitrogen and the resultant reaction mixture was heated and refluxed for 4 hours. To the reaction mixture, a saturated aqueous sodium hydrogen carbonate solution was added. The mixture was extracted with ethyl acetate. The organic phase was washed with water, then washed with brine, and dried over anhydrous sodium sulfate. From the organic phase, the solvent was distilled off under reduced pressure and the resultant residue was purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate) to give the title compound. Optical resolution of the solid of the title compound was performed by preparative chromatography (column: CHIRALPAK OD-H (2 cm×25 cm) manufactured by Daicel Chemical Industries, Ltd., eluent; hexane: ethanol=1:1 (V/V), flow rate: 8 mL/minute) to give each diastereomer of the title compound. The retention time was determined by LC/MS.

Primary fraction (21 mg, retention time 5.92 minutes, diastereomer a: Example 54 (A)-a)

Secondary fraction (31 mg, retention time 5.83 minutes, diastereomer b: Example 54 (A)-b)

Example 55

Synthesis of 3-hydroxy-5-(4-(((R)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide

<Step 1> Synthesis of (S)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-ol

In accordance with the method in (Example 51) <Step 1>, the title compound (1.0 g) was obtained as a brown solid from (1S)-4-hydroxy-2,3-dihydro-1H-inden-1-ol (4.0 g) that was commercially available or could be obtained by a known method and (2-methylpyridin-3-yl)boronic acid (4.4 g).

<Step 2> Synthesis of (R)-6-methyl-2-(4-(((R)-4-((2-methylpyridin-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,3,6,2-dioxazaborocane-4,8-dione

In accordance with the method in (Example 1) <Step 3>, the title compound (0.35 g) was obtained as a colorless amorphous from the compound (0.40 g) obtained in (Example 55) <Step 1> and the compound (0.40 g) obtained in (Reference Example 1).

<Step 3> Synthesis of 3-hydroxy-5-(4-(((R)-4-((2-methylpyridine-3-yl)oxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazole 1-oxide (A)

In accordance with the method in (Example 1) <Step 6>, the title compound (0.13 g) was obtained as a white solid using the enantiomer A (Example 1-5 (A)) (0.16 g) obtained in (Example 1) <Step 5> from the compound (0.33 g) obtained in (Example 55) <Step 2>.

289

<Step 4> Synthesis of 3-hydroxy-5-(4-(((R)-4-(m-tolyloxy)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)

In accordance with the method in (Example 51) <Step 4>, the title compound was obtained from the compound (0.10 g) obtained in (Example 55) <Step 3> and by the following preparative chromatography, each diastereomer (primary fraction (diastereomer-a: Example 55 (A)-a): 31 mg, secondary fraction (diastereomer-b: Example 55 (A)-b): 15 mg) thereof was obtained.

Example 56

Optical Resolution of 5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)isothiazolidin-3-one 1-oxide (A)

In accordance with the method in (Example 1) <Step 5>, optical resolution of the compound in (Example 29) was performed.

column: CHIRALCEL OD-3 manufactured by Daicel Chemical Industries, Ltd., mobile phase; ethanol (containing 0.05% diethylamine):carbon dioxide=5:95 to 40:60
The retention time was determined by UPLC/MS.

Primary fraction (1.4 g, retention time 1.13 minutes, diastereomer a: Example 56 (A)-a)

Secondary fraction (1.1 g, retention time 1.14 minutes, diastereomer b: Example 56 (A)-b)

Example 57

Synthesis of 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

In accordance with the method in (Example 30) <Step 3>, the title compound (48 mg) was obtained as a white solid from the diastereomer a (Example 56 (A)-a) obtained in (Example 56) (50 mg).

The compounds of (Example 58) to (Example 69) below were synthesized in the same manner as in (Example 57) in accordance with the method in (Example 30) <Step 3> and among them, the compound of (Example 58) was synthesized from the diastereomer b (Example 56 (A)-b) obtained in (Example 56) and the compounds of (Example 59) to (Example 69) were synthesized using the diastereomer a (Example 56 (A)-a) obtained in (Example 56) and a corresponding boronic acid or boronic acid ester.

Example 58

5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-b

Example 59

5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

290

Example 60

5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

Example 61

3-hydroxy-5-(4-(((R)-4-(4-methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 62

3-hydroxy-5-(4-(((R)-4-(2-methyl-6-(3-(methylsulfonyl)propoxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 63

3-hydroxy-5-(4-(((R)-4-(6-methoxy-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 64

3-hydroxy-5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 65

3-hydroxy-5-(4-(((R)-4-(2-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 66

3-hydroxy-5-(4-(((R)-4-(o-tolyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-4,5-dihydroisothiazole 1-oxide (A)-a

Example 67

5-(4-(((R)-4-(5-fluoro-2-methylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

Example 68

5-(4-(((1R)-4-(2-fluoro-6-methoxyphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

Example 69

5-(4-(((R)-4-(2-ethoxy-5-fluorophenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-3-hydroxy-4,5-dihydroisothiazole 1-oxide (A)-a

The compounds shown below, the compounds of Structural Formulae 8 to 17 ((Example 1P) to (Example 157P)), compounds that can be obtained in combination of Partial Structural Formulae shown in the aspect [1-19-1] to the aspect [1-19-2], salts of them, solvates of them, and optical

291

isomers of them can also be easily synthesized by using Production Methods above, the methods described in Examples, methods known by a person skilled in the art, or modified methods of them.

5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazolidin-3-one;

5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-chloro-4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-chloro-4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-chloro-4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[4-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one;

5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one;

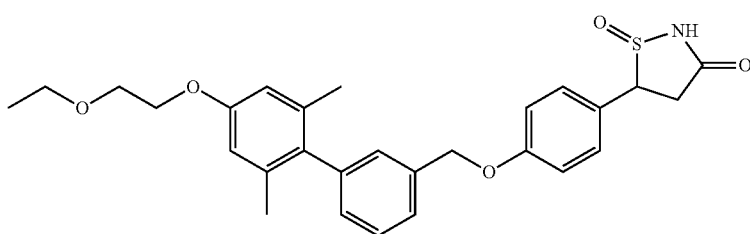
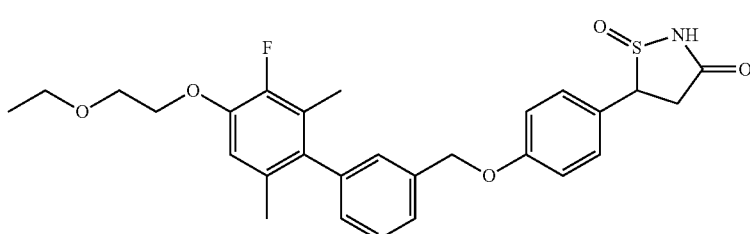
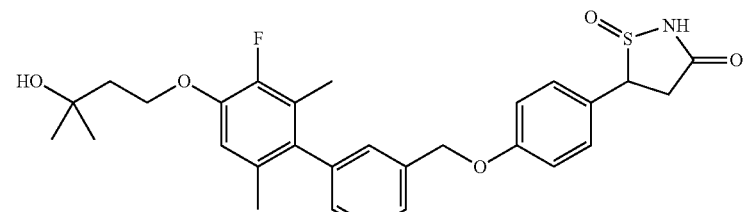
292

5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2,6-thiadiazinan-3-one (Example 14P);

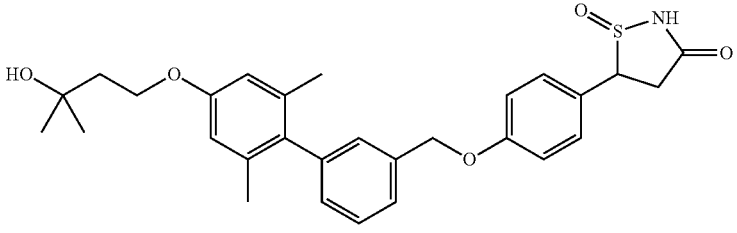
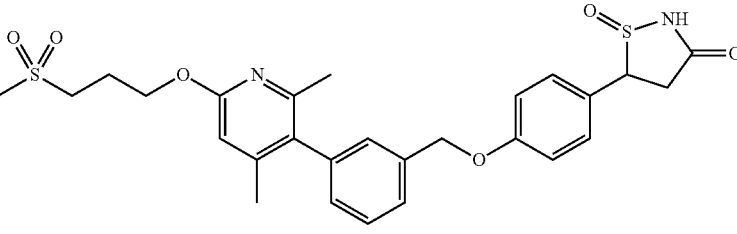
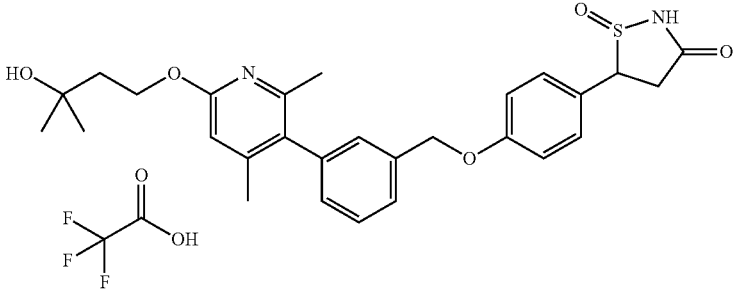
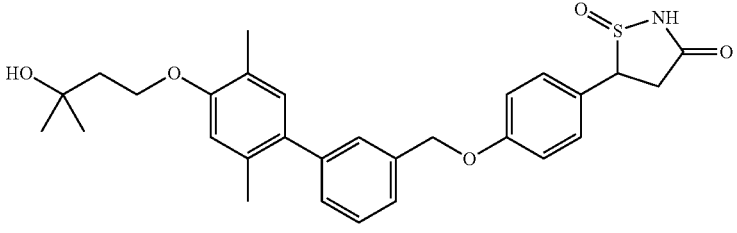
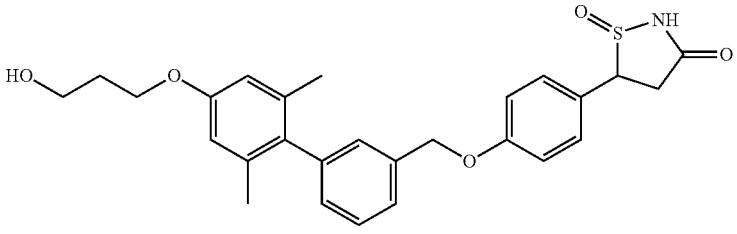
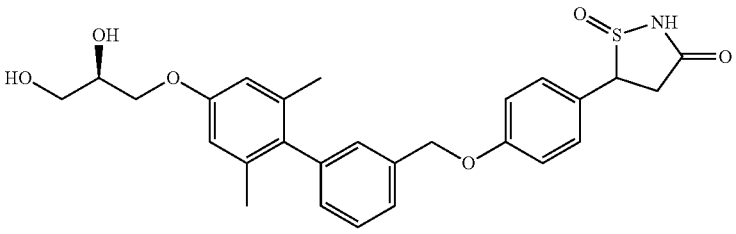
5-[4-[[3-[2,4-dimethyl-6-(3-methylsulfonylpropoxy)pyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one; and

5-(4-((3-(2,6-dimethylphenyl)phenyl)methoxy)phenyl)-1,1-dioxo-1,2-thiazolidin-3-one (Example 37P).

The structures of the final compounds synthesized in (Example 1) to (Example 35) above and the structures of the compounds in (Example 1P) to (Example 157P) are shown in the figures below (Structural Formulae I to 12). LC/MS data and NMR data (no mark: 400 MHz NMR, *: 300 MHz NMR) of these final compounds of Examples are also shown in Tables below (Tables 2, 3, 7, and 8). The structures of the intermediate compounds synthesized in Examples and the compounds of Reference Examples are shown in the figures below (Structural Formulae 13 to 19) and LC/MS data of these intermediate compounds and the compounds of Reference Examples are also shown in Tables below (Tables 4, 5, 6, 9, 10, 11, and 12). Here, with respect to the intermediate compound, for example, the compound obtained in Example 1 <Step 1> is expressed as "1-1".

Structural Formula 1	
Example No.	Structure
1	
2	
3	

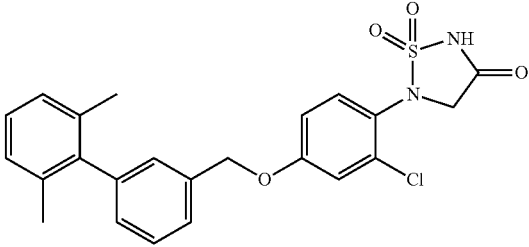
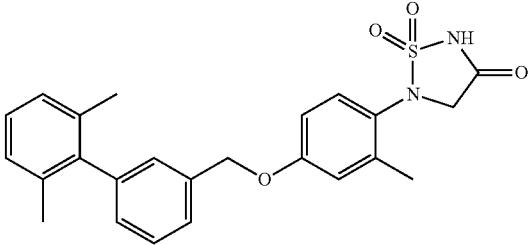
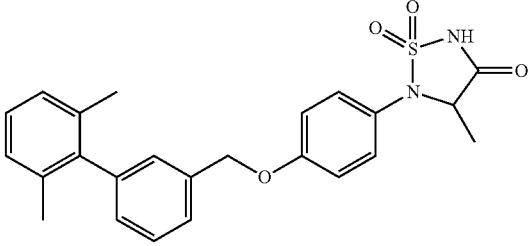
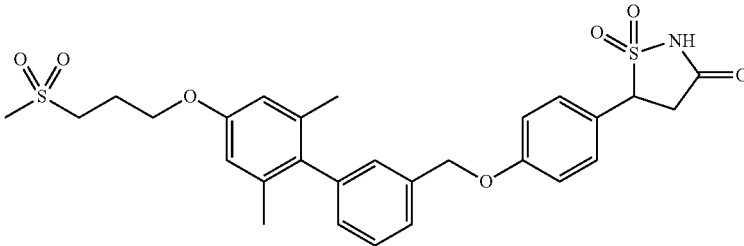
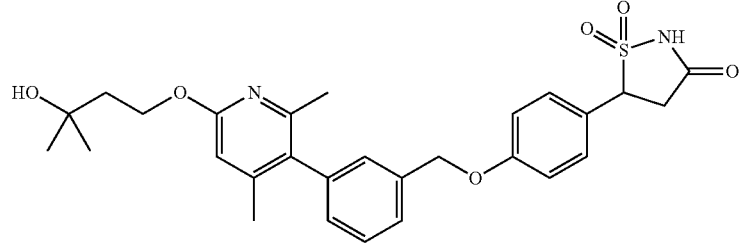
-continued

Structural Formula 1	
Example No.	Structure
4	
5	
6	
7	
8	
9	

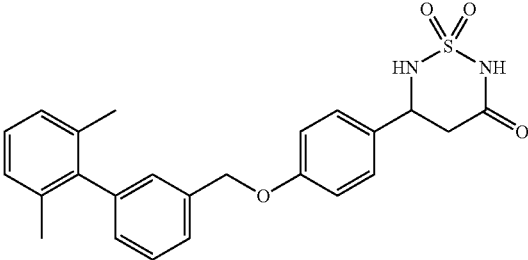
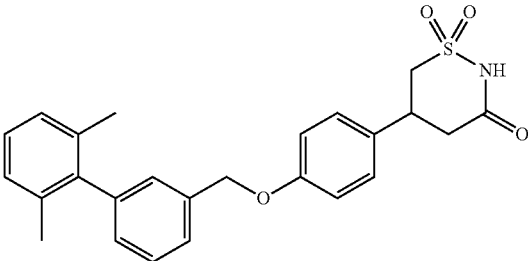
-continued

Structural Formula 1	
Example No.	Structure
10	
11	
12	
13	
14	
15	

-continued

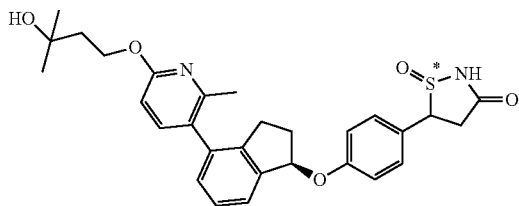
Structural Formula 1	
Example No.	Structure
16	
17	
18	
19	
20	

-continued

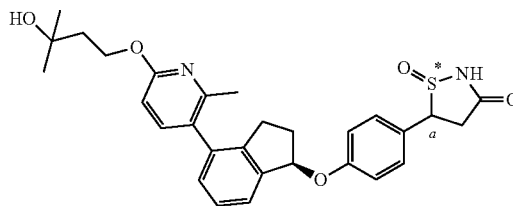
Structural Formula 1	
Example No.	Structure
21	
22	

Structural Formula 2

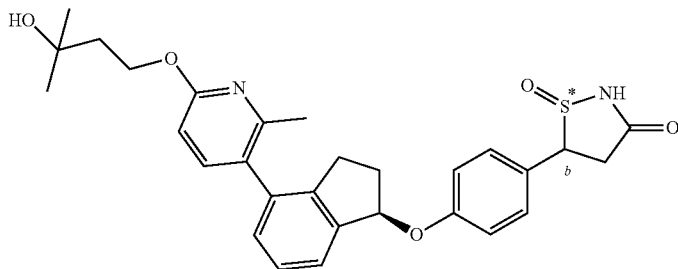
Example 23



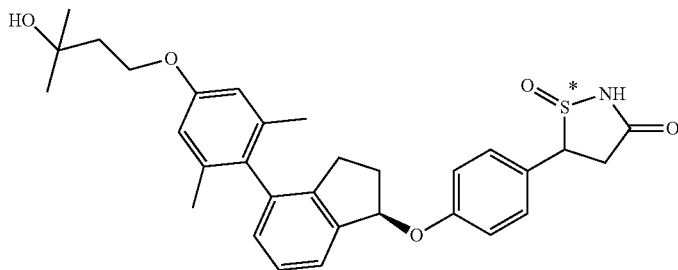
Example 23(A)-a



Example 23(A)-b



Example 24



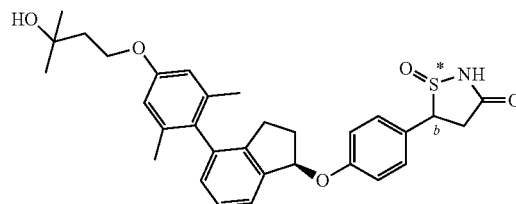
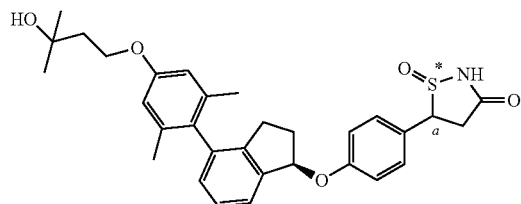
301

302

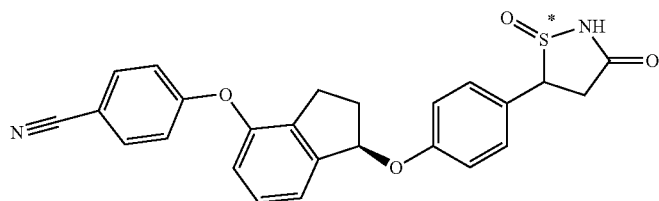
-continued

Example 24(A)-a

Example 24(A)-b

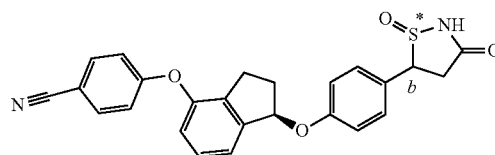
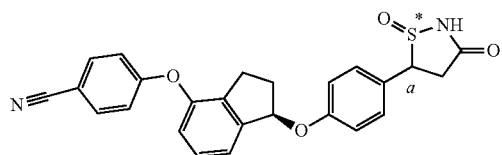


Example 25

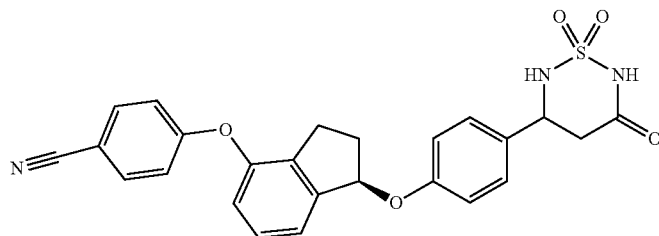


Example 25(A)-a

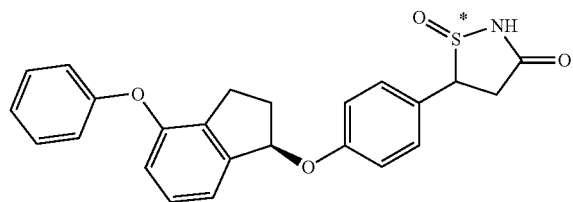
Example 25(A)-b



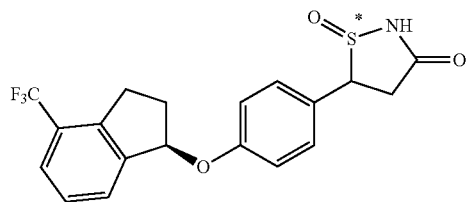
Example 26



Example 27

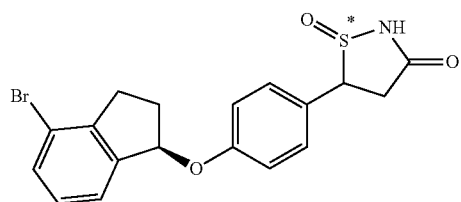


Example 28



Structural Formula 3

Example 29

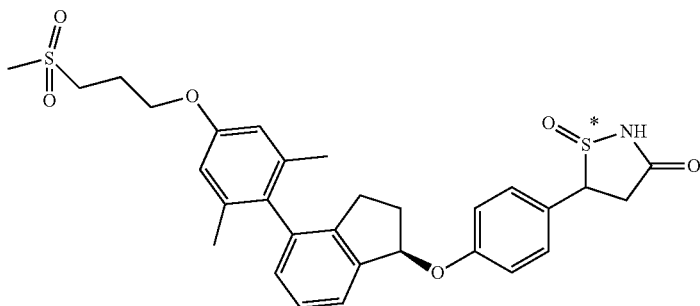


303

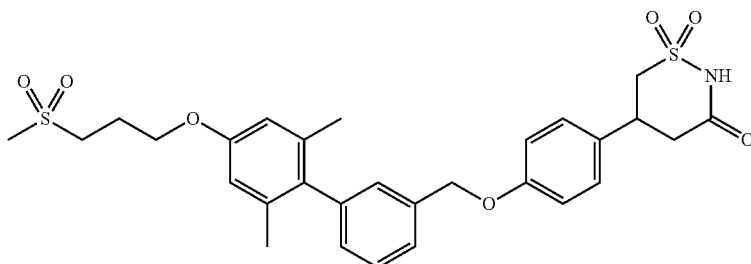
304

-continued

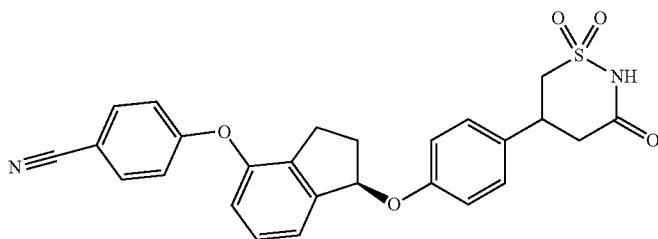
Example 30



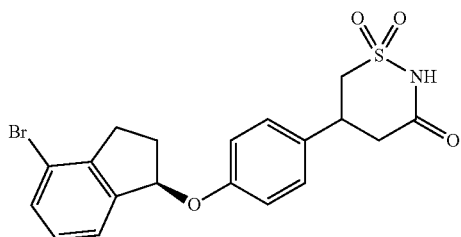
Example 31



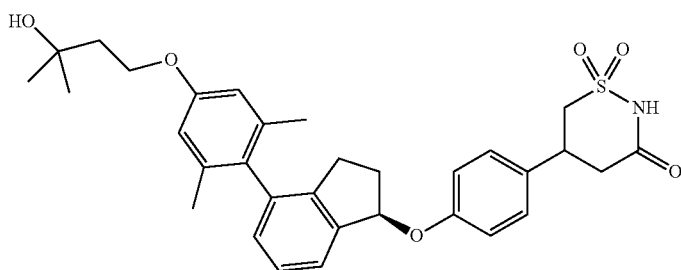
Example 32



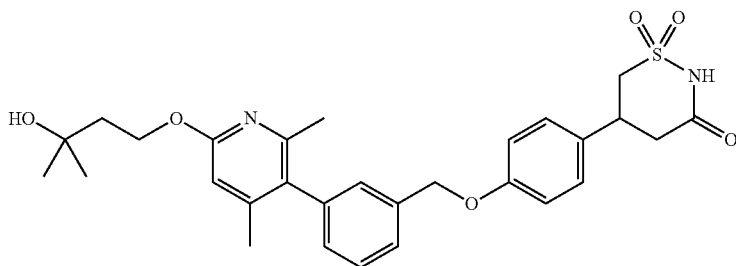
Example 33



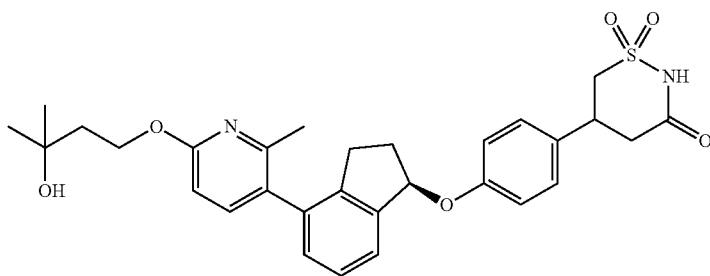
Example 34



Example 35

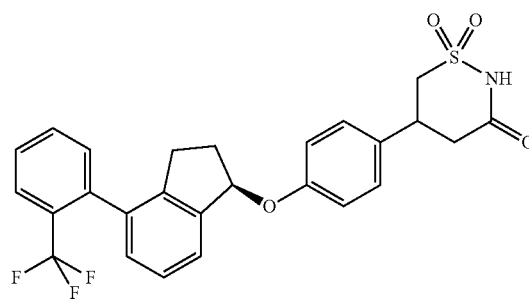
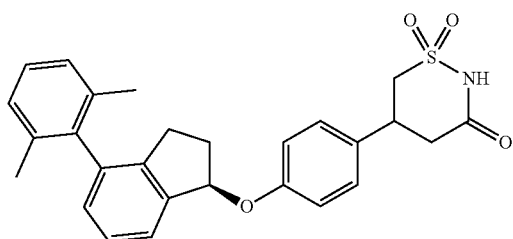


Example 36

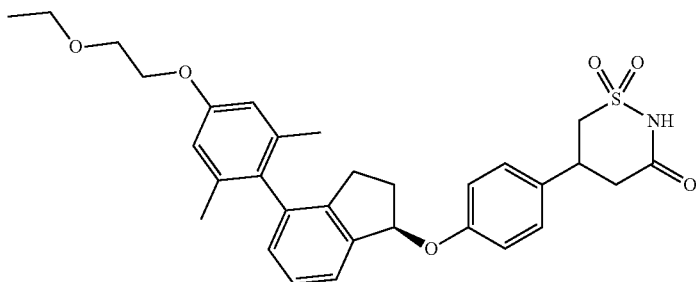


Example 37

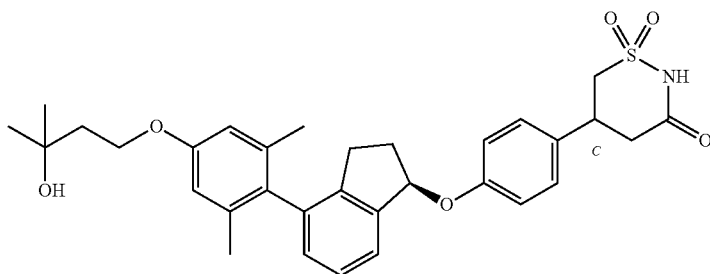
Example 38



Example 39



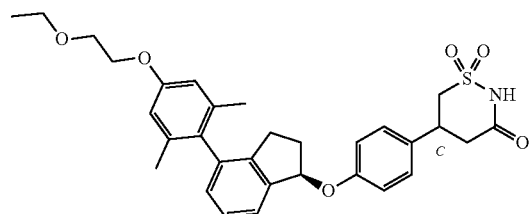
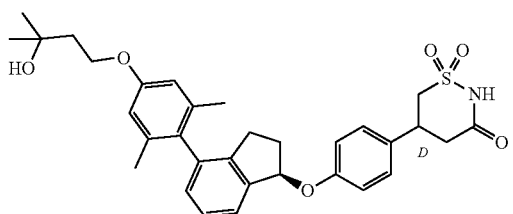
Example 40



Structural Formula 4

Example 41

Example 42



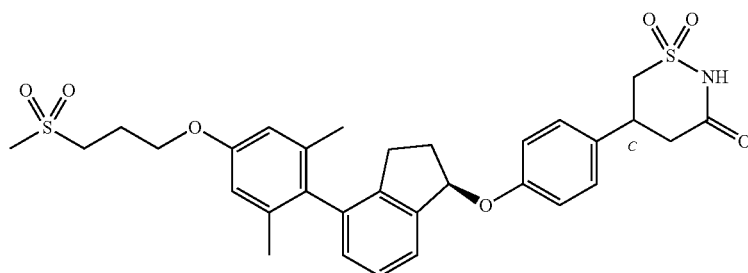
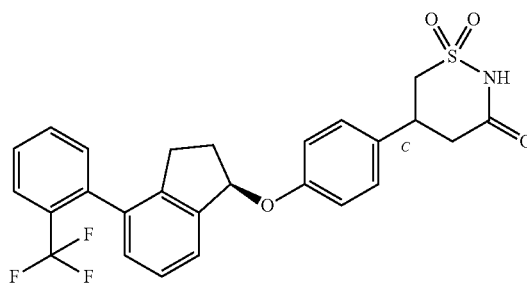
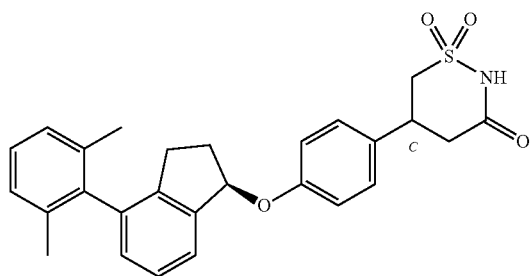
307

308

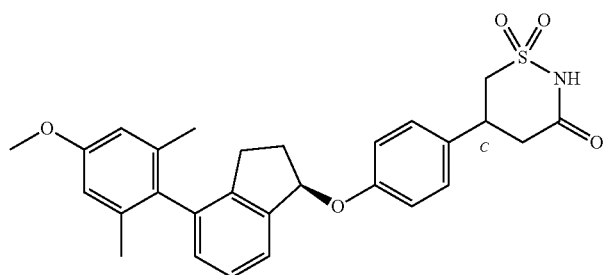
-continued

Example 43

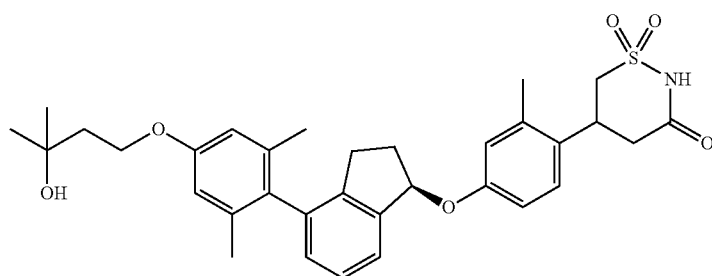
Example 44



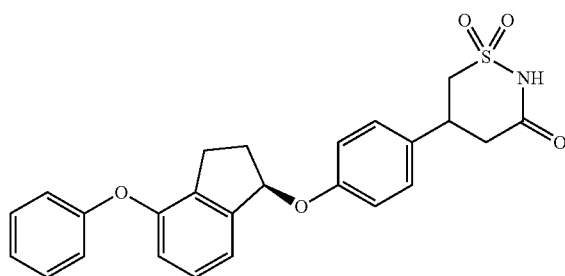
Example 45



Example 46



Example 47

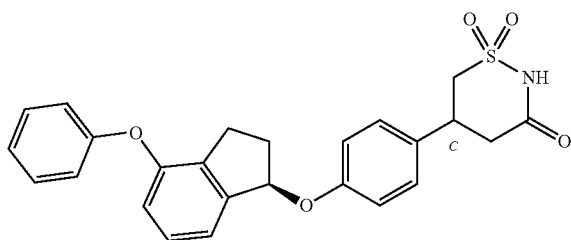


Example 48

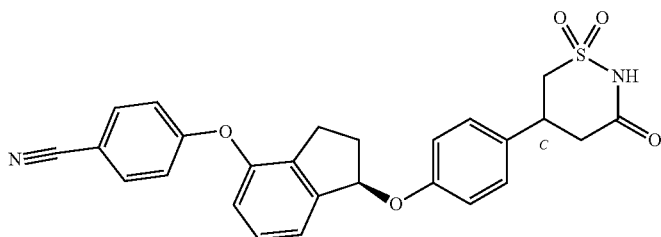
309

310

-continued

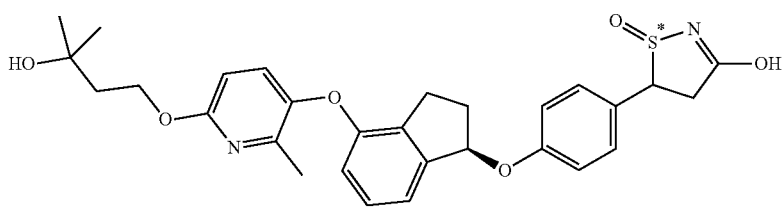


Example 49

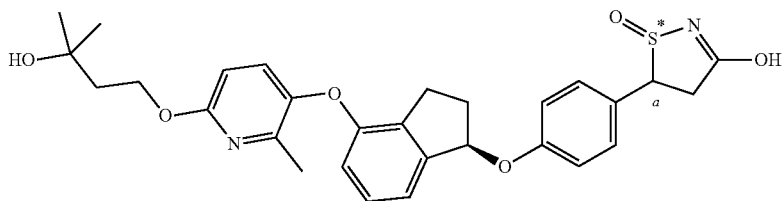


Example 50

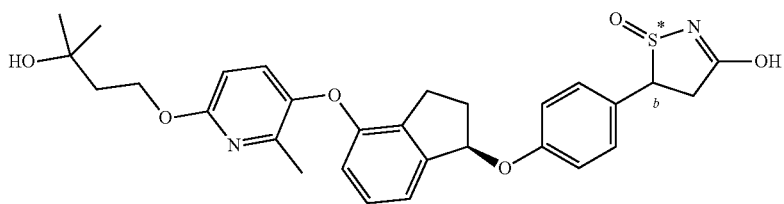
Structural Formula 5



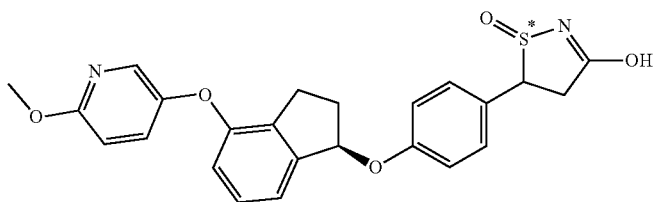
Example 51



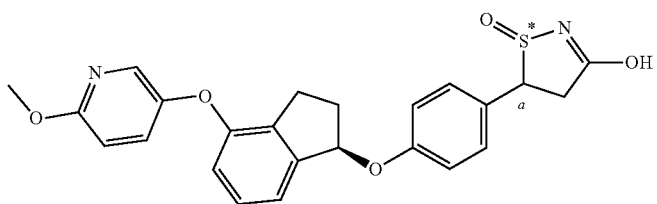
Example 51(A)-a



Example 51(A)-b



Example 52



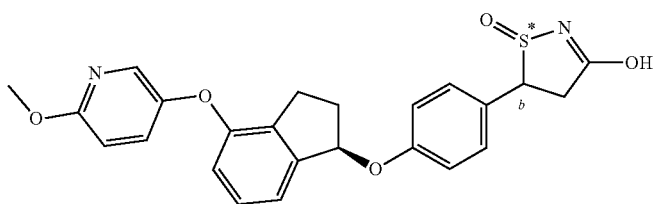
Example 52(A)-a

311

312

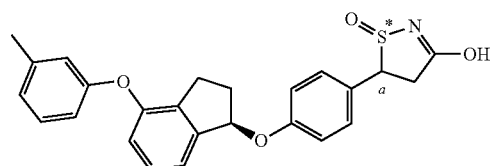
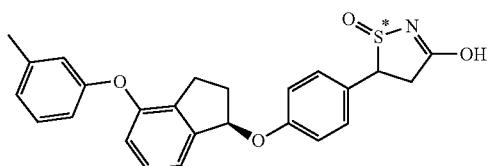
-continued

Example 52(A)-b

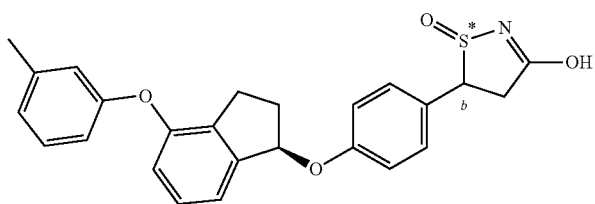


Example 53

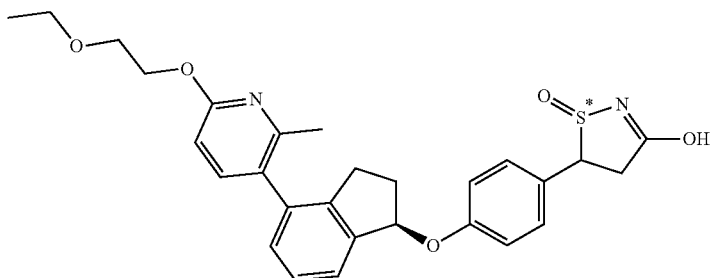
Example 53(A)-a



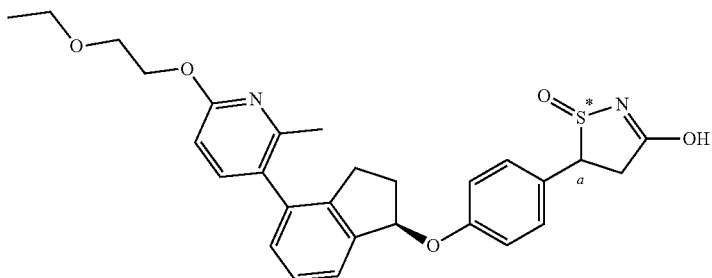
Example 53(A)-b



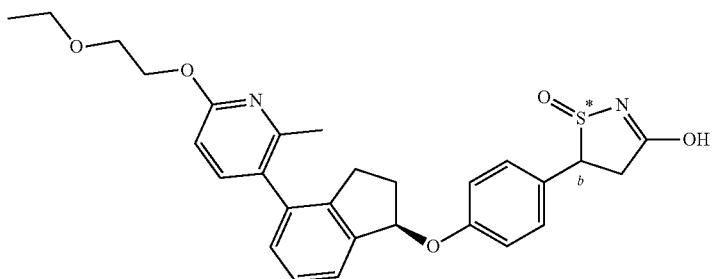
Example 54



Example 54(A)-a



Example 54(A)-b



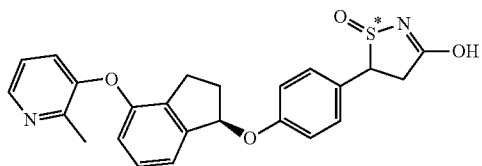
313

314

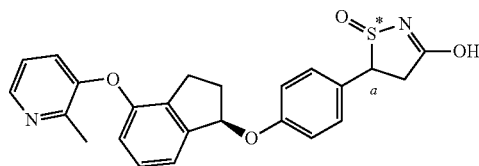
-continued

Structural Formula 6

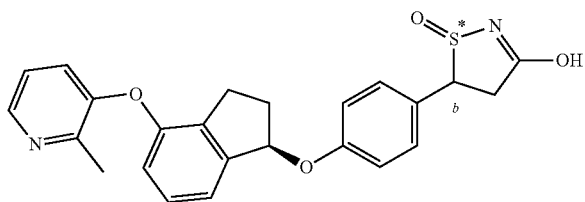
Example 55



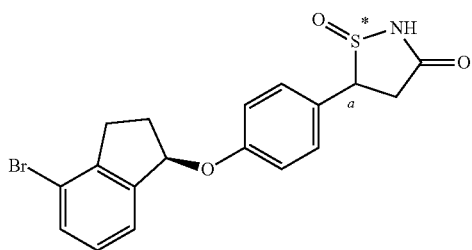
Example 55(A)-a



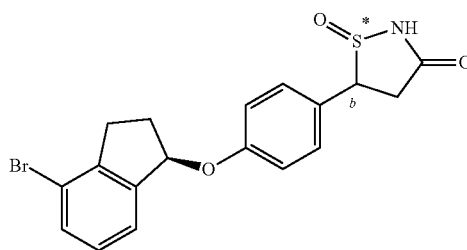
Example 55(A)-b



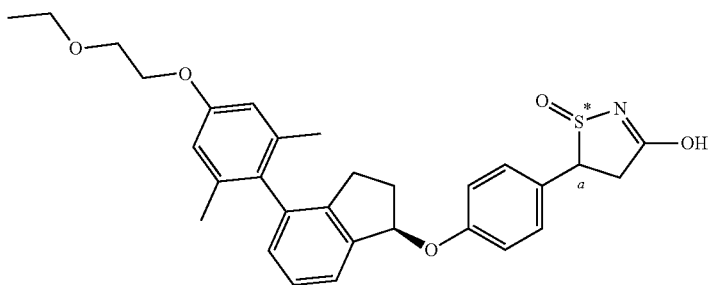
Example 56(A)-a



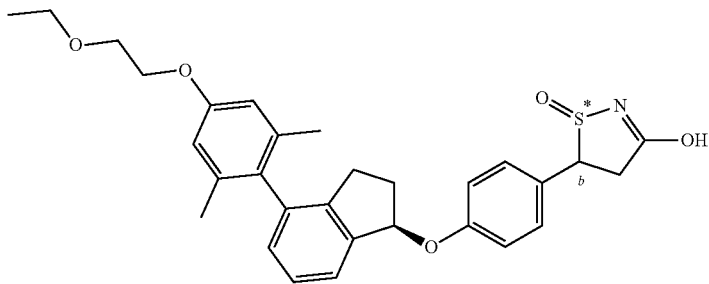
Example 56(A)-b



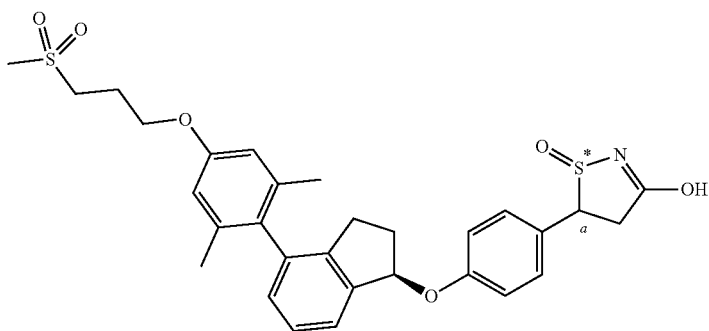
Example 57



Example 58



Example 59



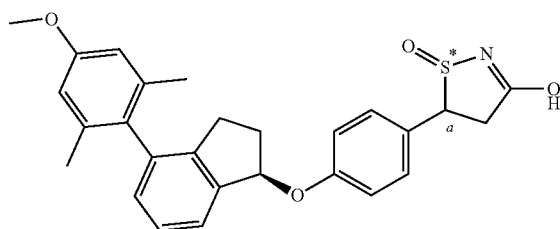
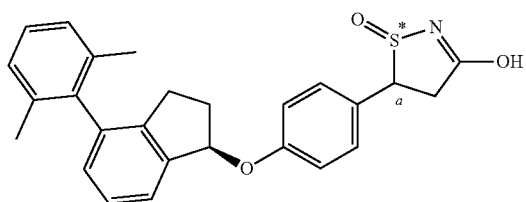
315

316

-continued

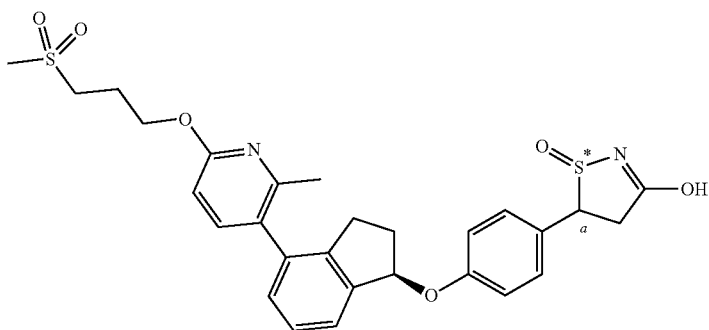
Example 60

Example 61

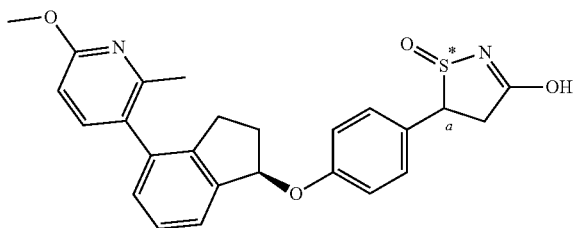


Structural Formula 7

Example 62

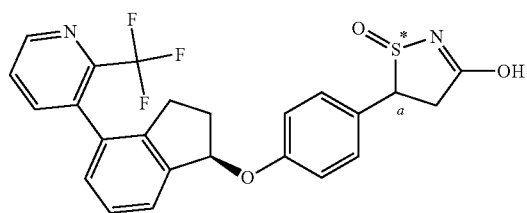
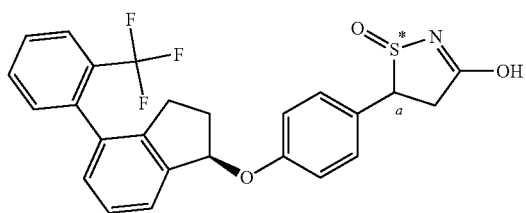


Example 63



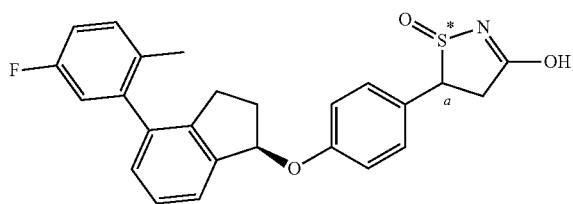
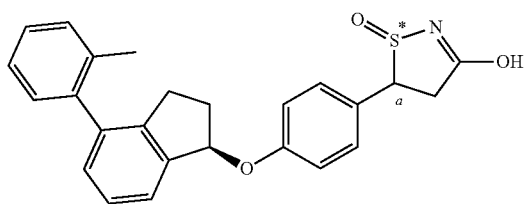
Example 64

Example 65



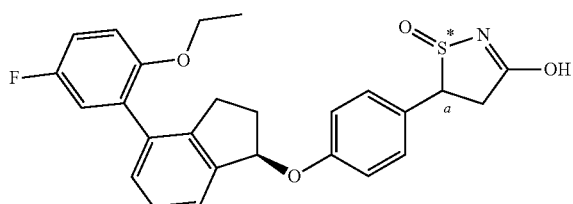
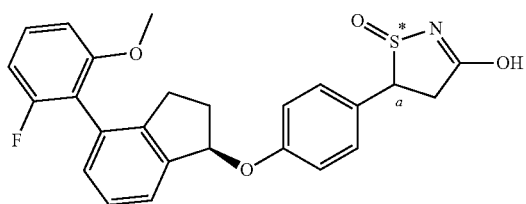
Example 66

Example 67



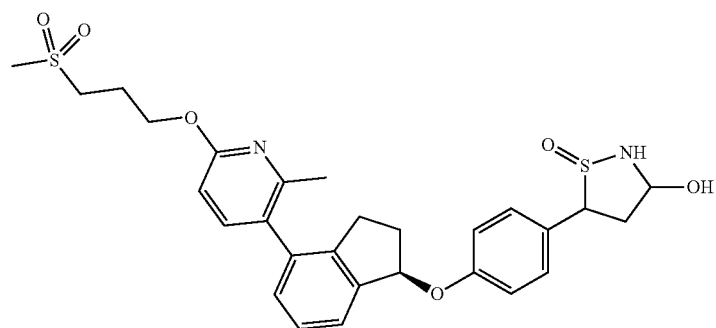
Example 68

Example 69

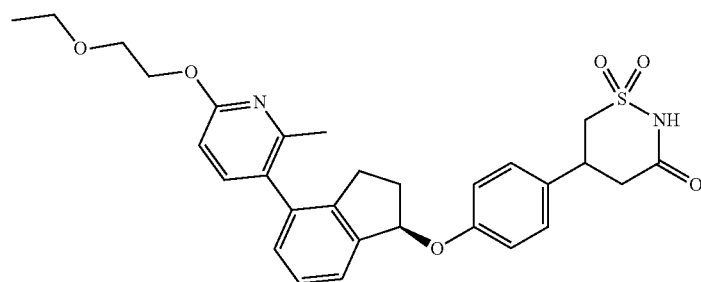


-continued

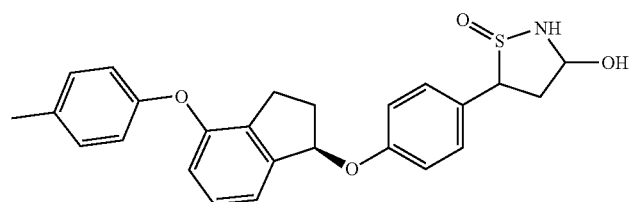
Structural Formula 8



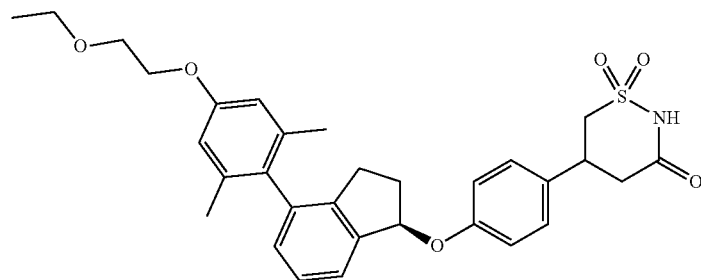
Example 1P



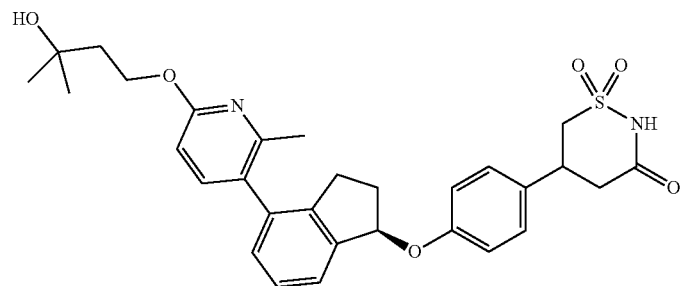
Example 2P



Example 3P



Example 4P



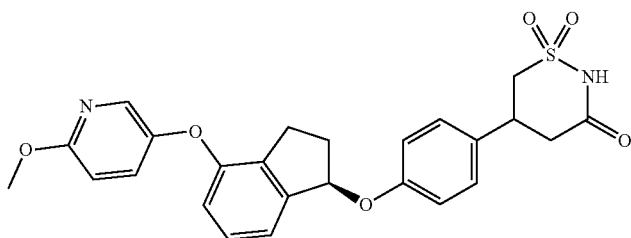
Example 5P

319

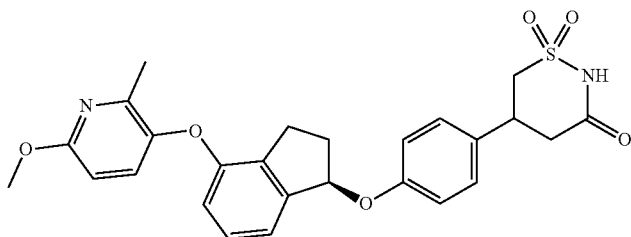
320

-continued

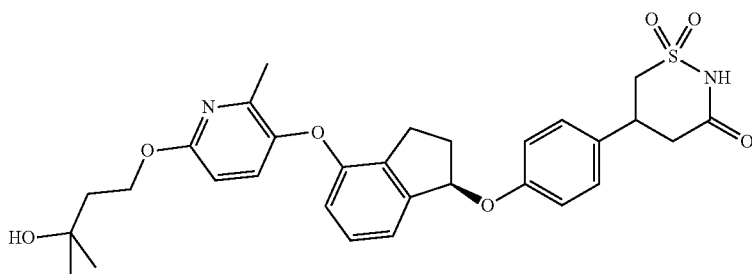
Example 6P



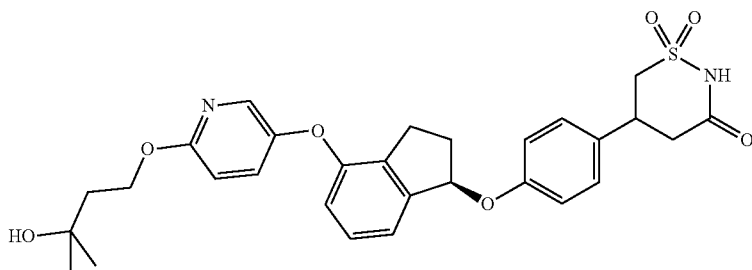
Example 7P



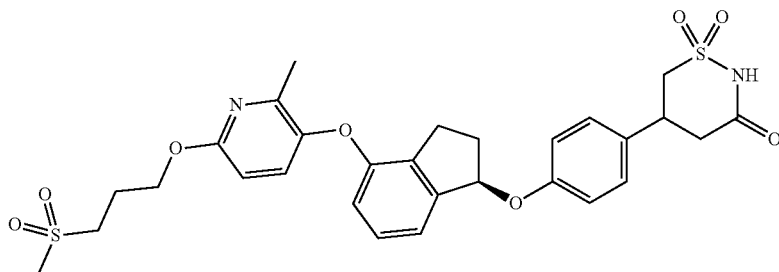
Example 8P



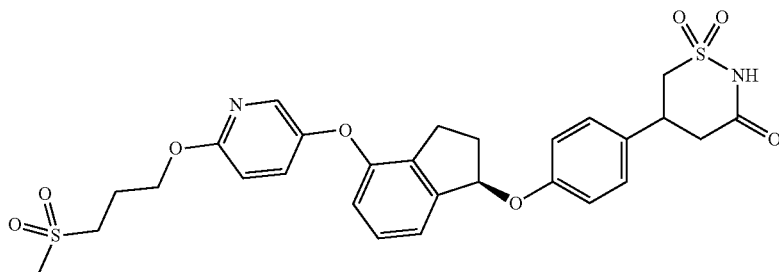
Example 9P



Example 10P



Example 11P

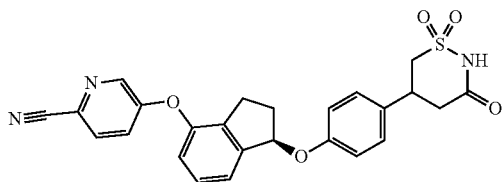


321

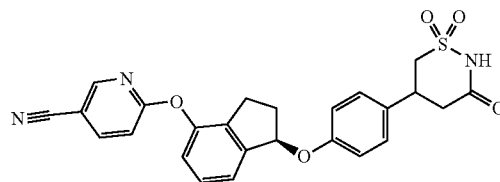
322

-continued

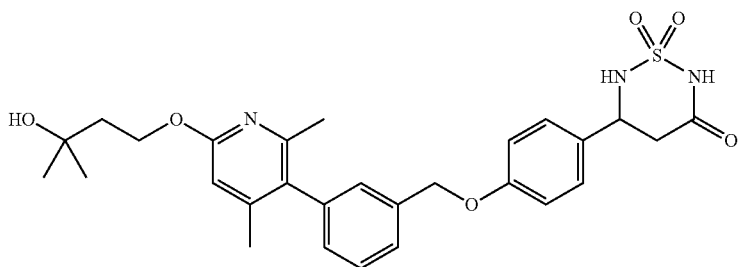
Example 12P



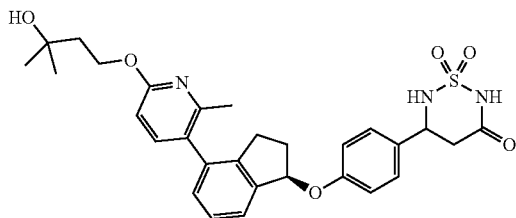
Example 13P



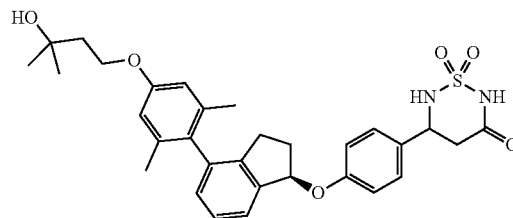
Example 14P



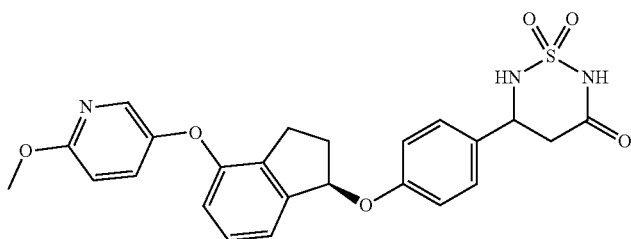
Example 15P



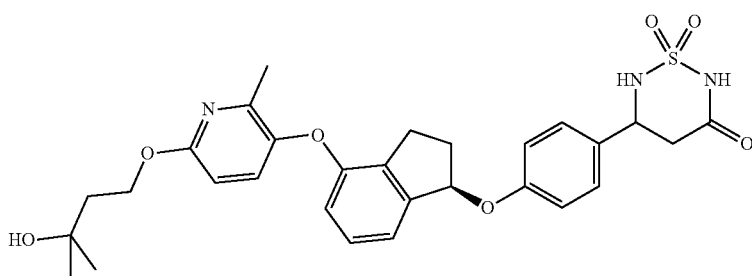
Example 16P



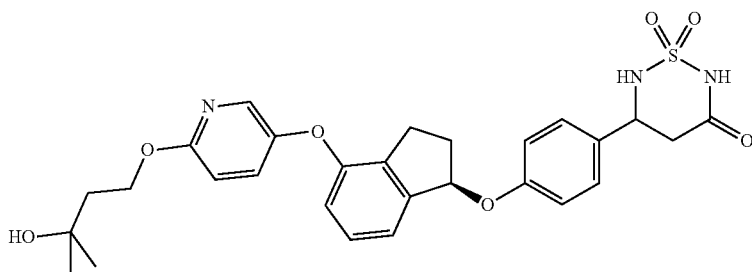
Structural Formula 9



Example 17P



Example 18P



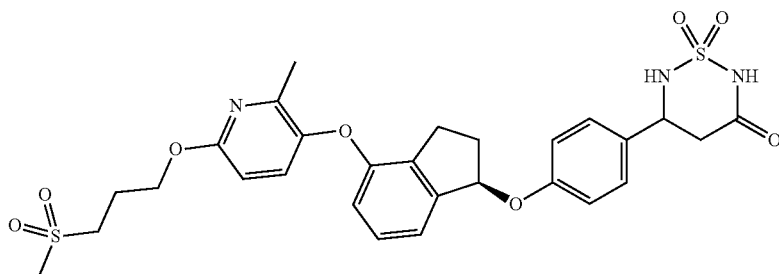
Example 19P

323

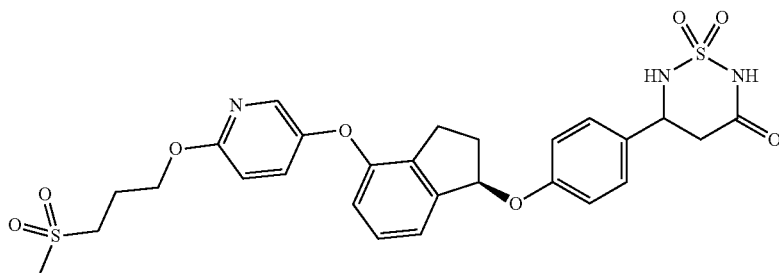
324

-continued

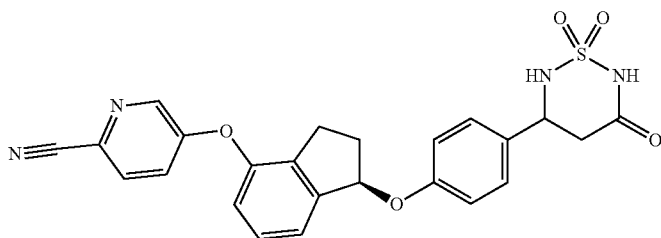
Example 20P



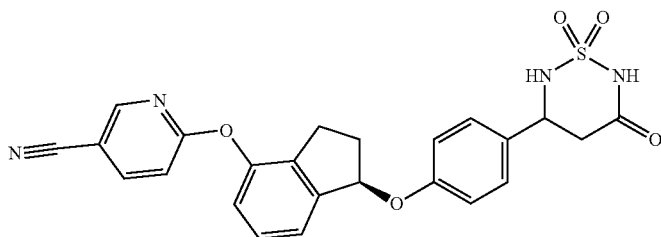
Example 21P



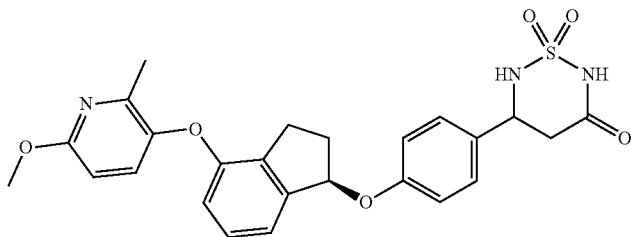
Example 22P



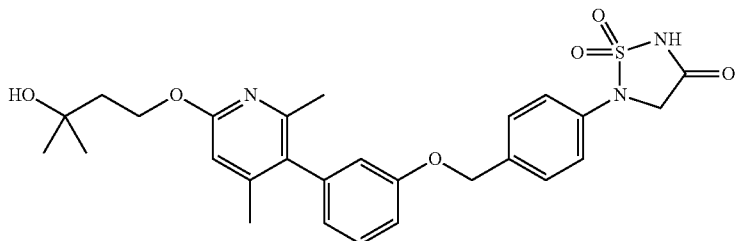
Example 23P



Example 24P



Example 25P

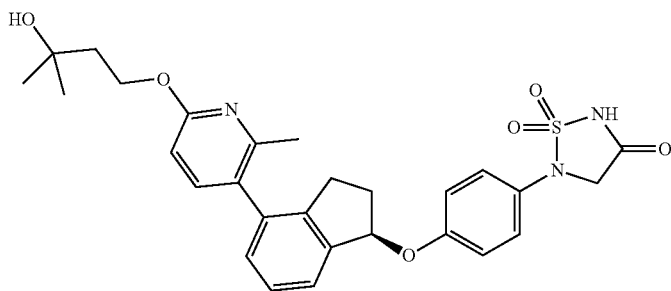


325

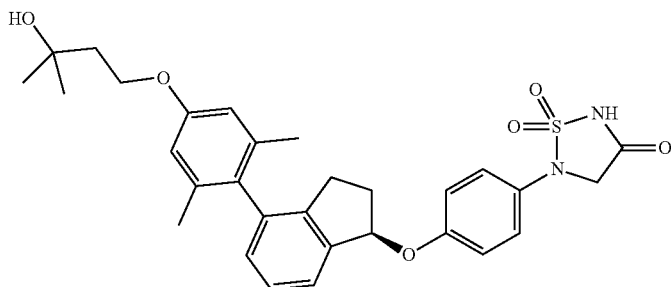
326

-continued

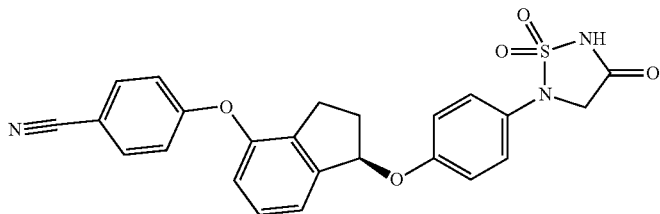
Example 26P



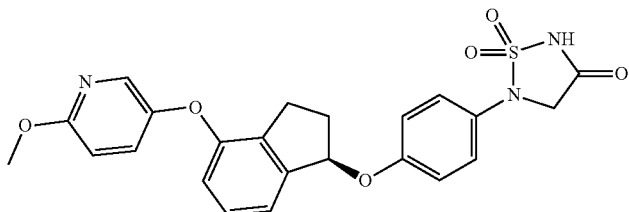
Example 27P



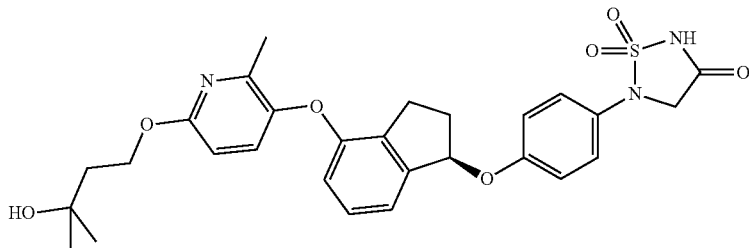
Example 28P



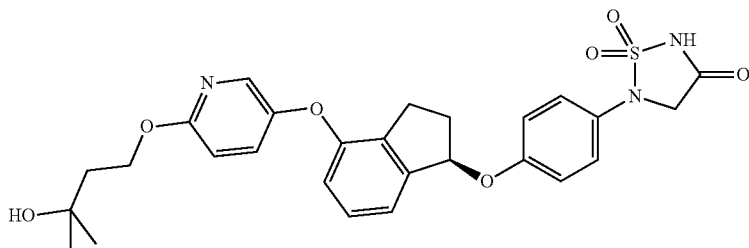
Example 29P



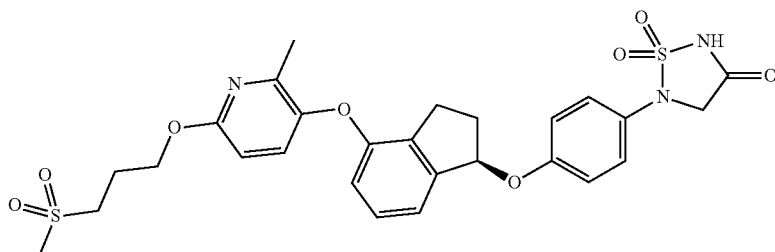
Example 30P



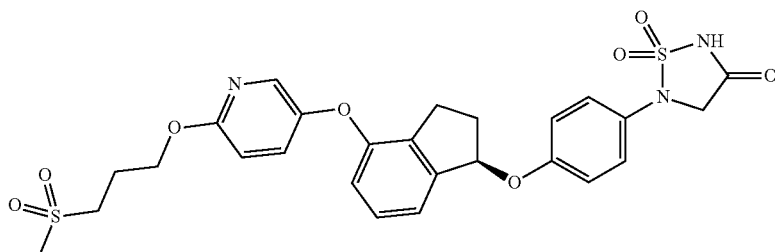
Example 31P



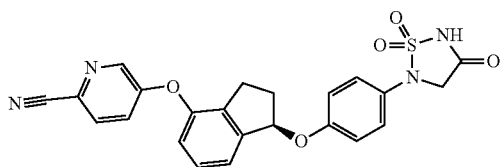
Example 32P



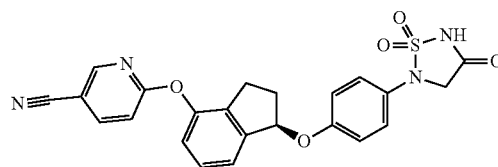
Structural Formula 10



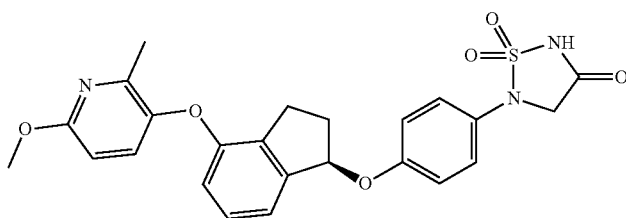
Example 33P



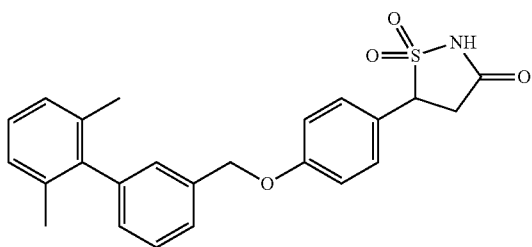
Example 34P



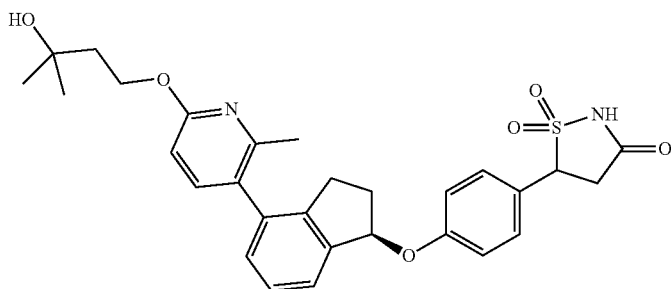
Example 35P



Example 36P



Example 37P



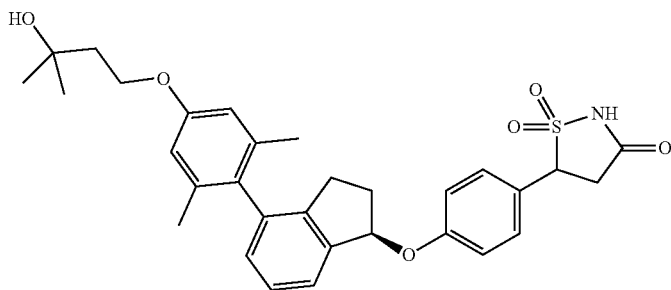
Example 38P

329

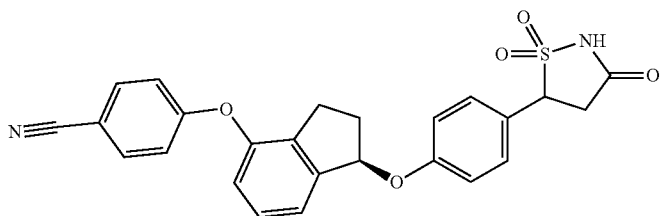
330

-continued

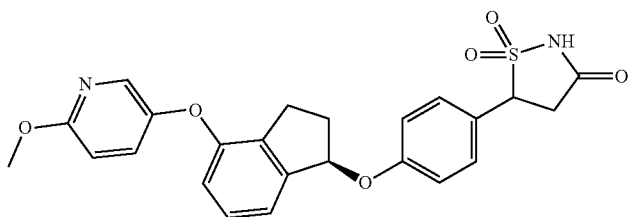
Example 39P



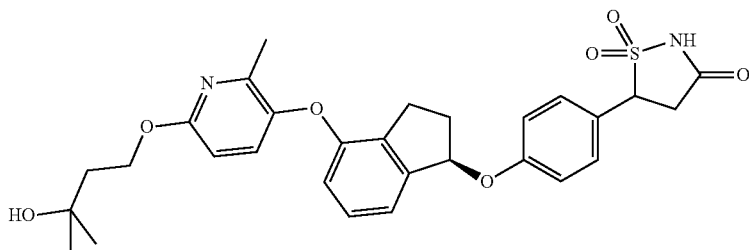
Example 40P



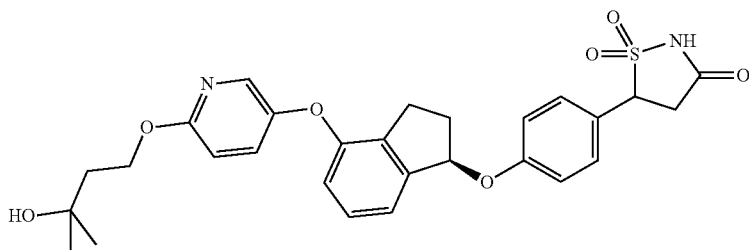
Example 41P



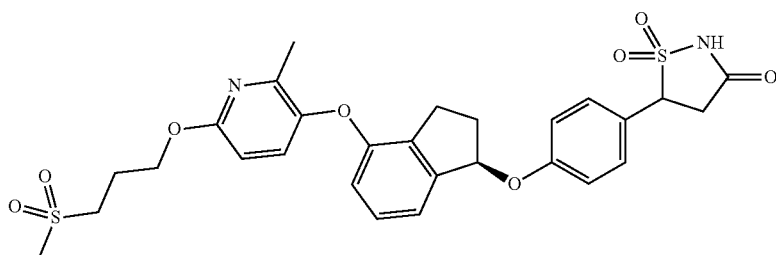
Example 42P



Example 43P



Example 44P

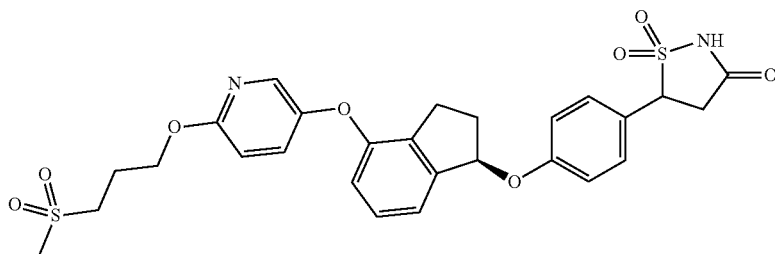


331

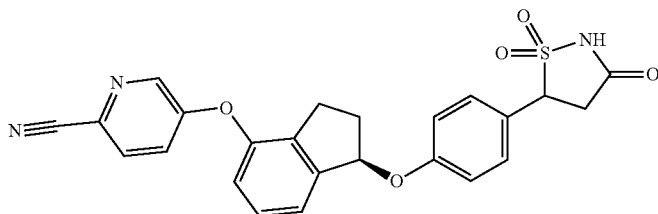
332

-continued

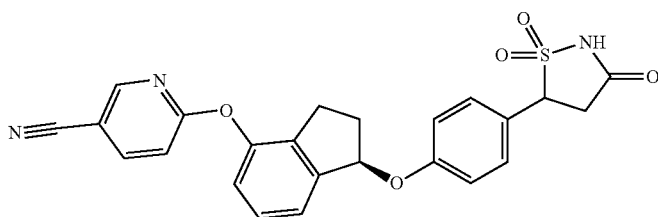
Example 45P



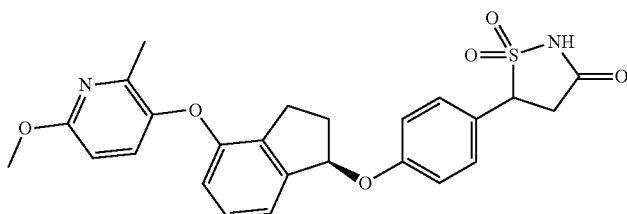
Example 46P



Example 47P

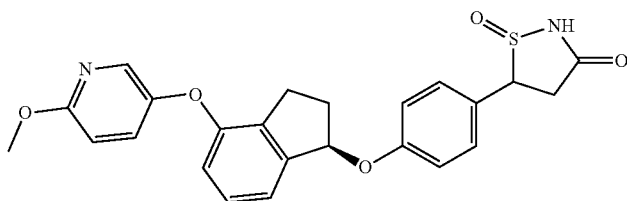


Example 48P

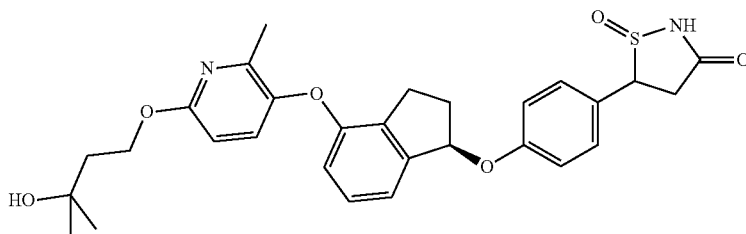


Structural Formula 11

Example 49P



Example 50P

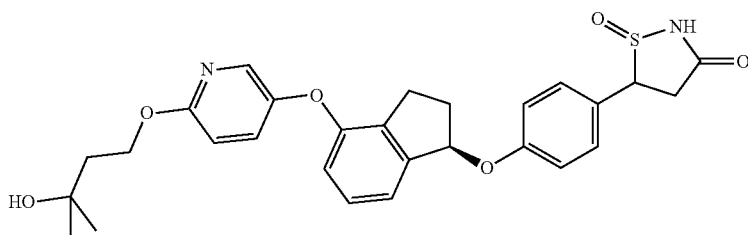


333

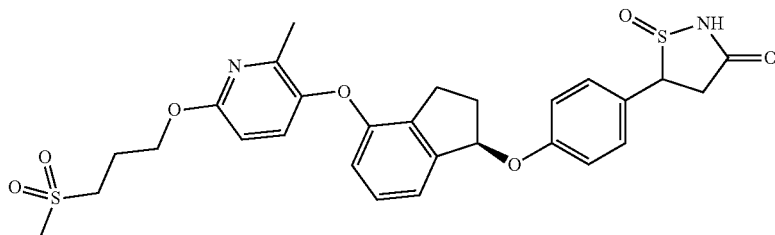
334

-continued

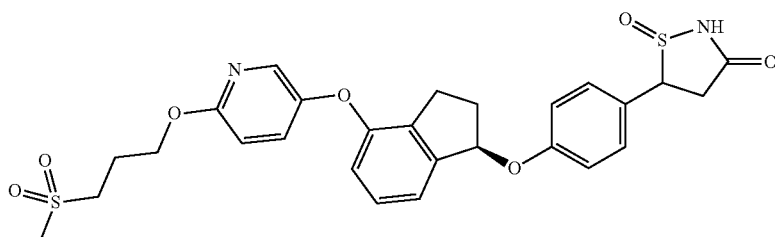
Example 51P



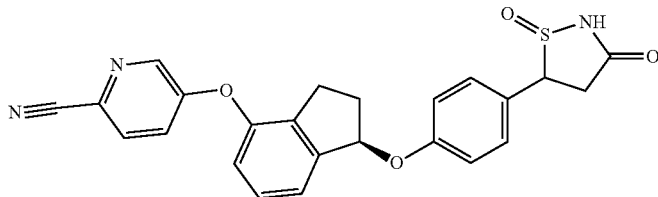
Example 52P



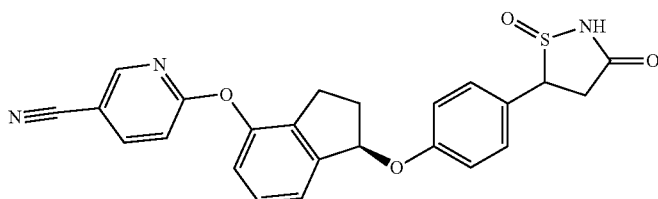
Example 53P



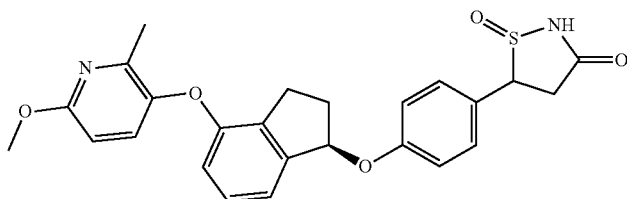
Example 54P



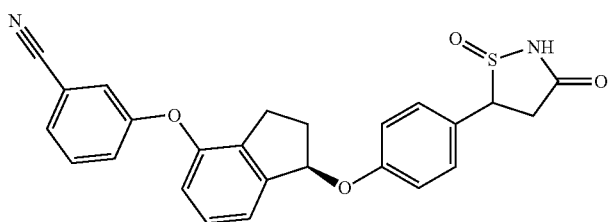
Example 55P



Example 56P

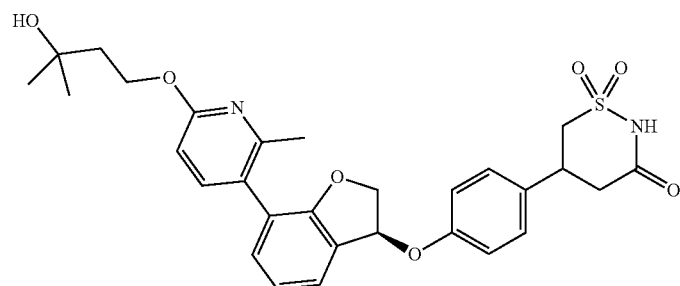


Example 57P

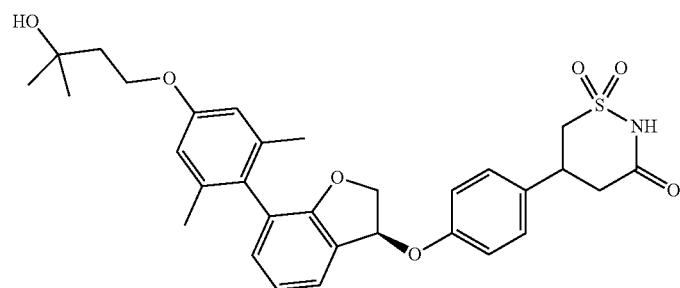


-continued

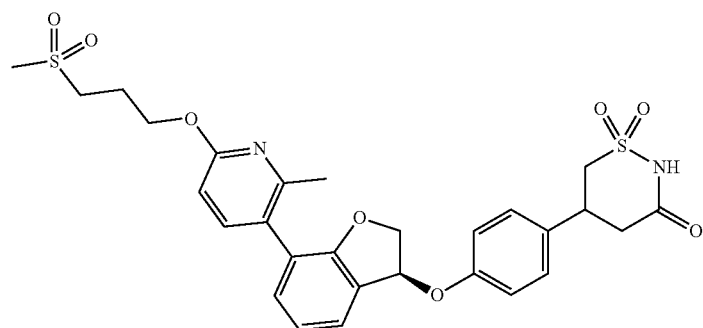
Structural Formula 12



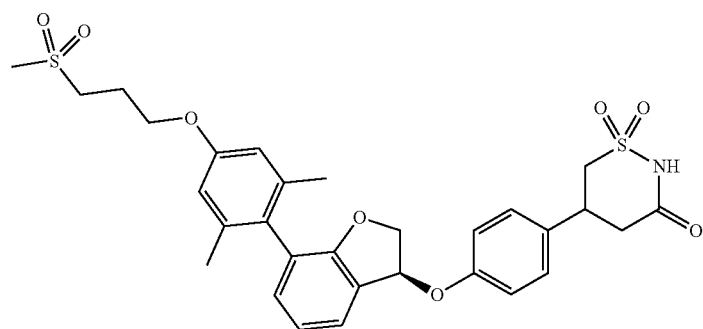
Example 58P



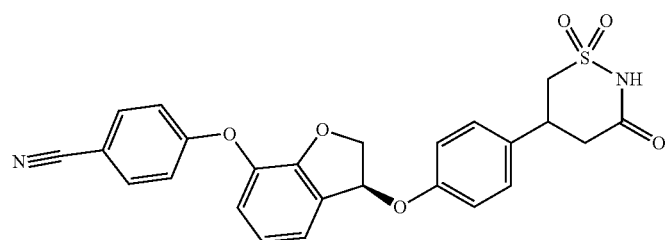
Example 59P



Example 60P

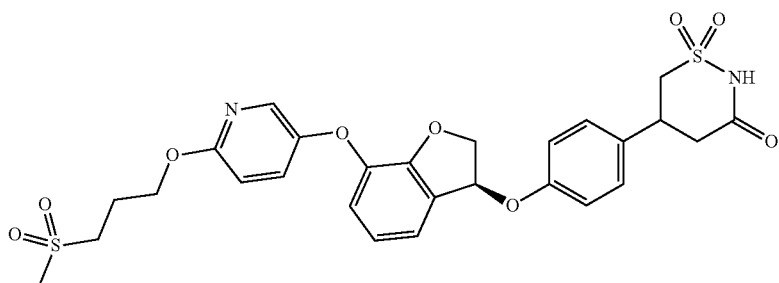
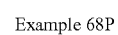
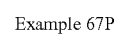
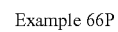
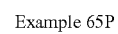
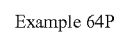


Example 61P



Example 62P

Example 63P



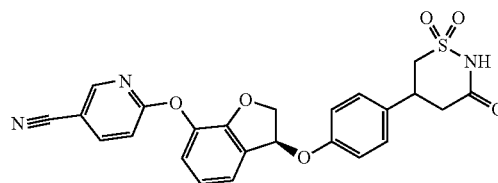
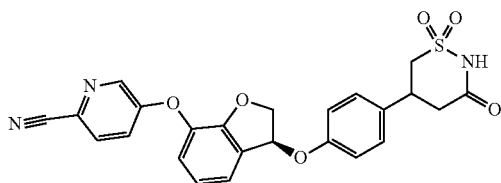
339

340

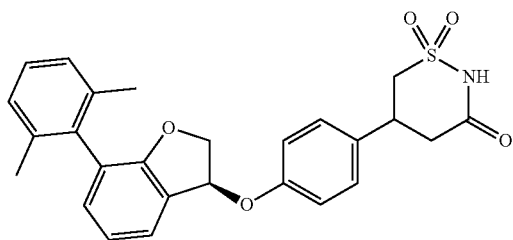
-continued

Example 69P

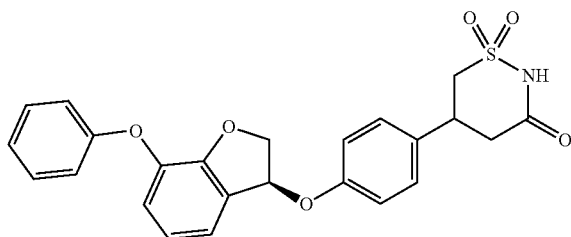
Example 70P



Example 71P

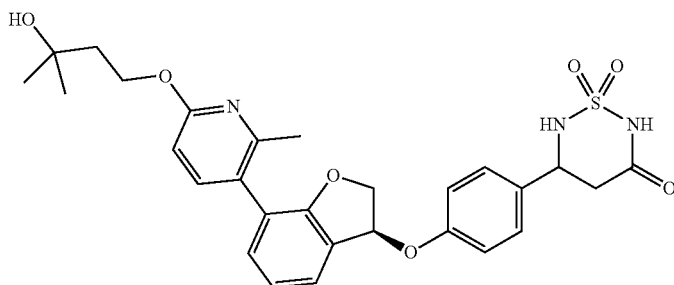


Example 72P

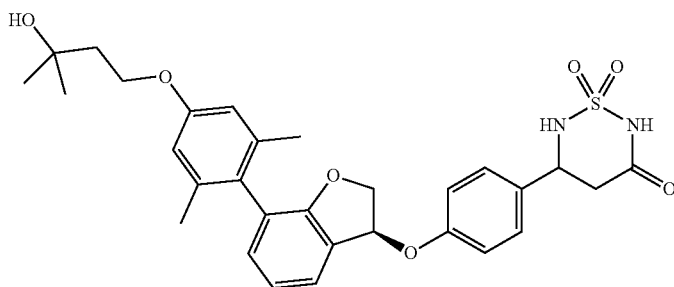


Structural Formula 13

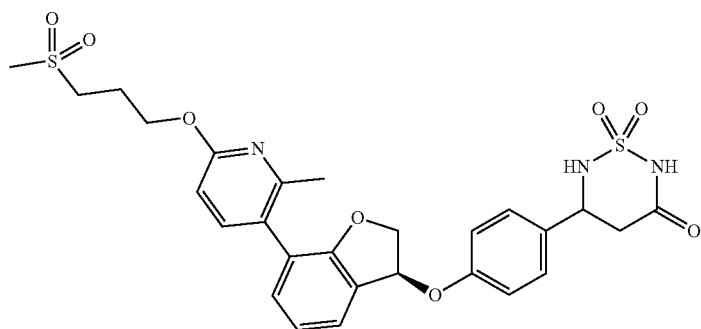
Example 73P



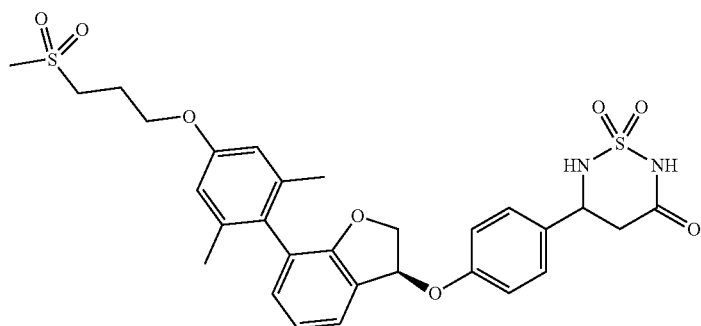
Example 74P



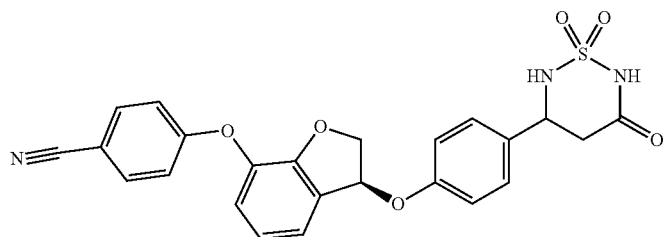
Example 75P



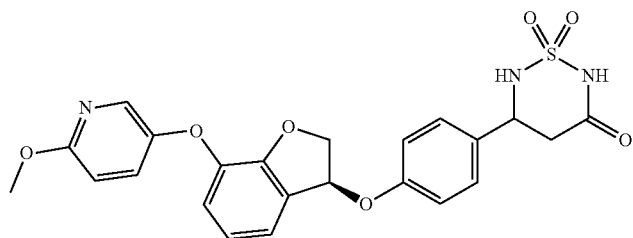
Example 76P



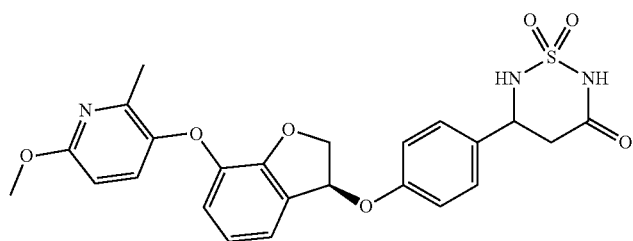
Example 77P



Example 78P



Example 79P

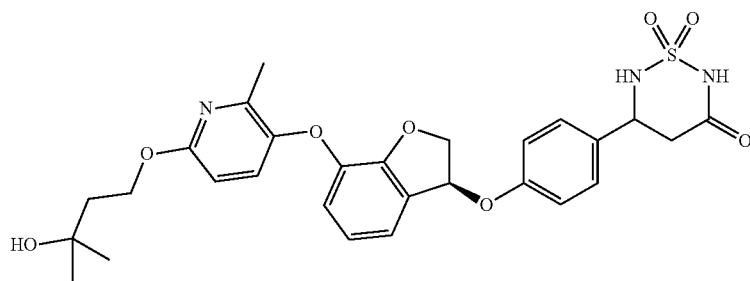


343

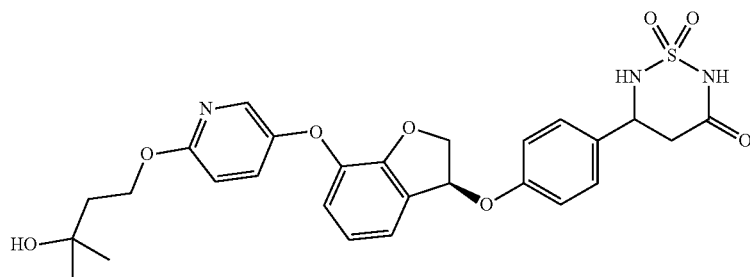
344

-continued

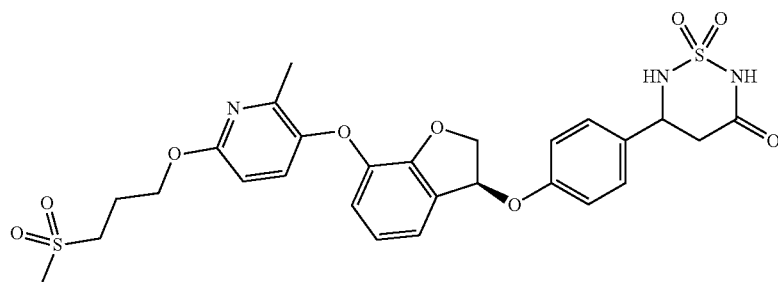
Example 80P



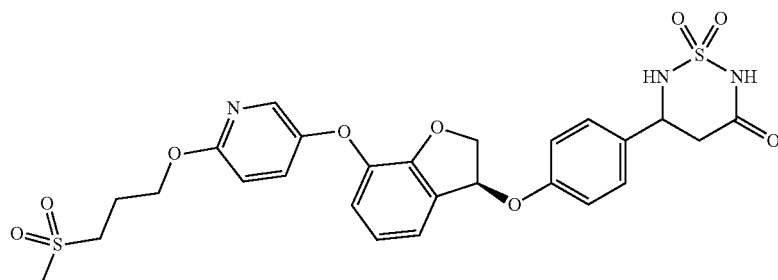
Example 81P



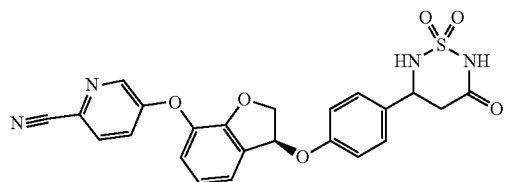
Example 82P



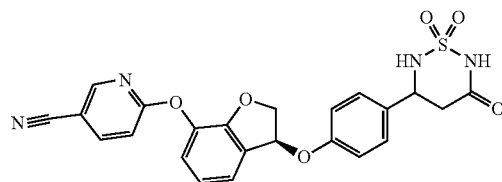
Example 83P



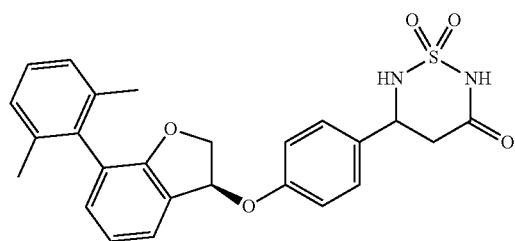
Example 84P



Example 85P



Example 86P

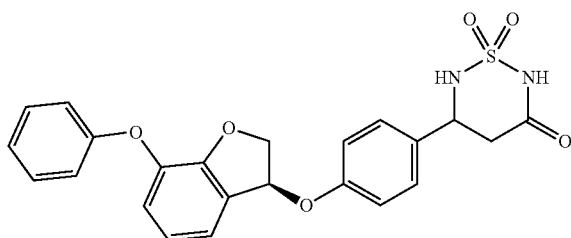


345

346

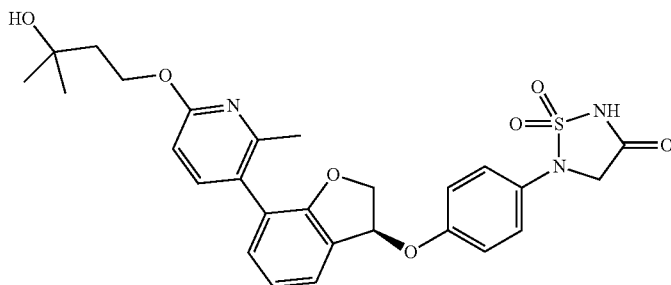
-continued

Example 87P

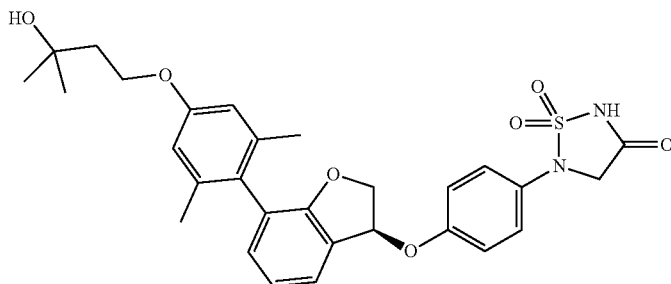


Structural Formula 14

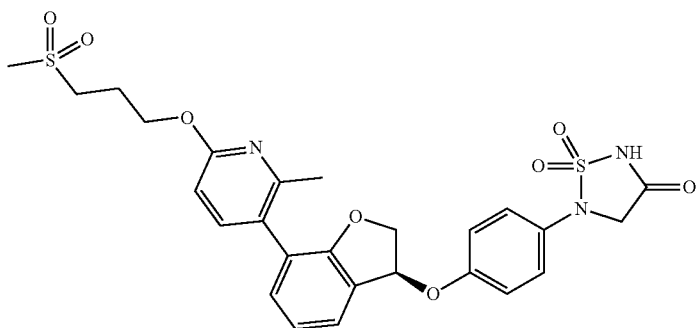
Example 88P



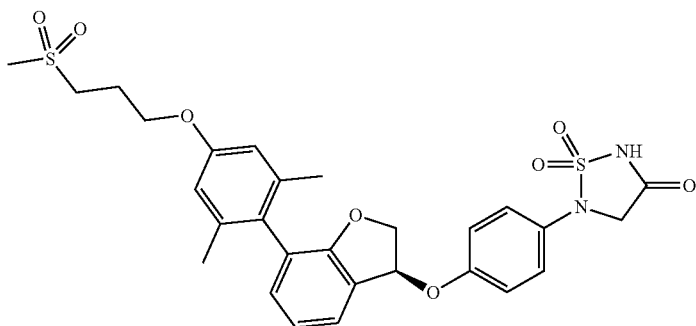
Example 89P



Example 90P

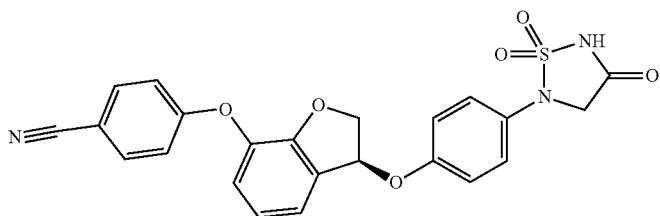


Example 91P

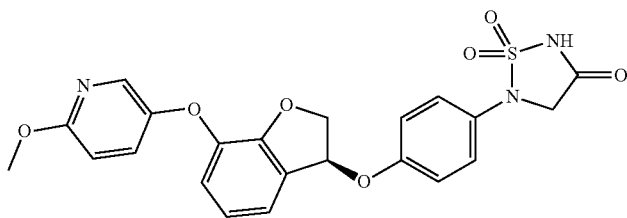


-continued

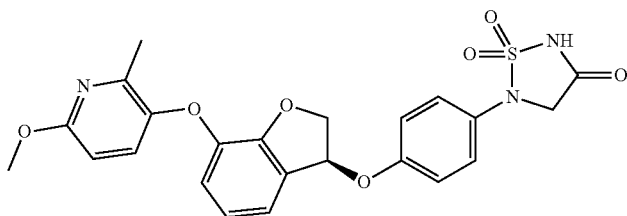
Example 92P



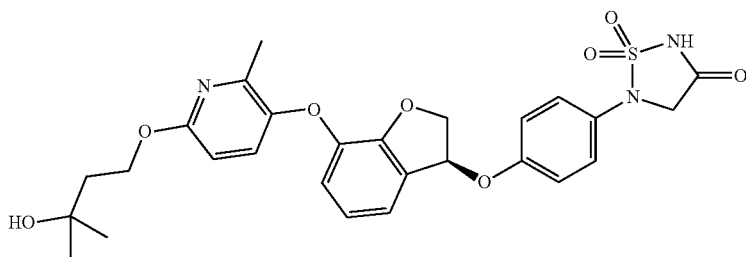
Example 93P



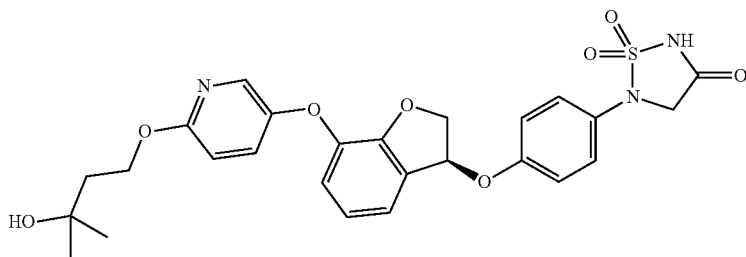
Example 94P



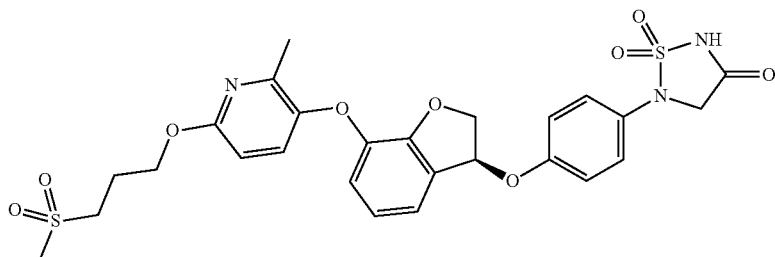
Example 95P



Example 96P



Example 97P

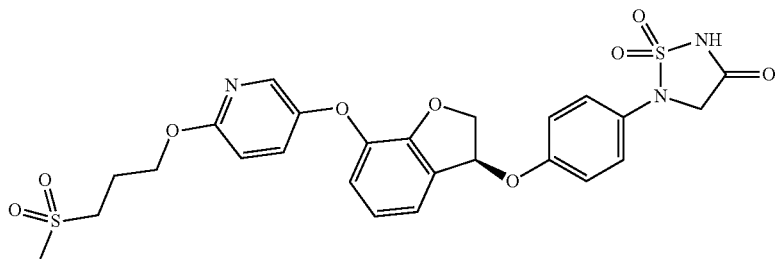


349

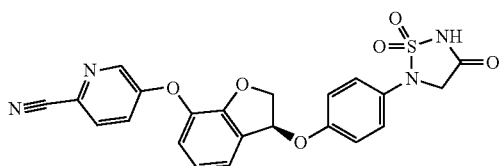
350

-continued

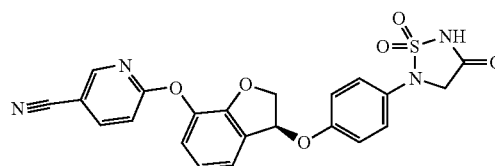
Example 98P



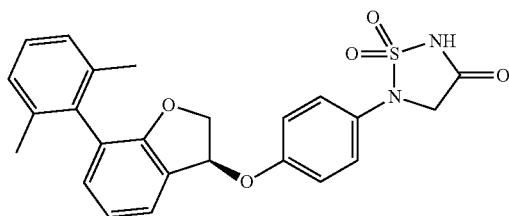
Example 99P



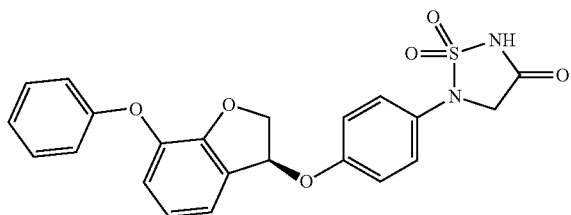
Example 100P



Example 101P

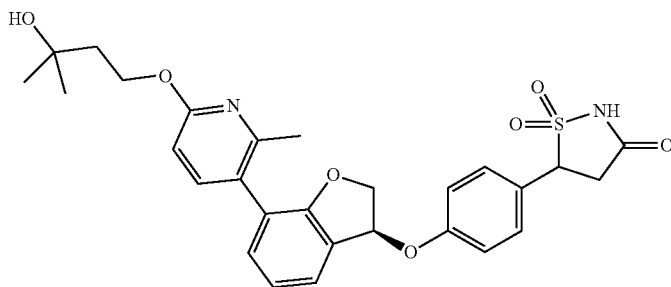


Example 102P

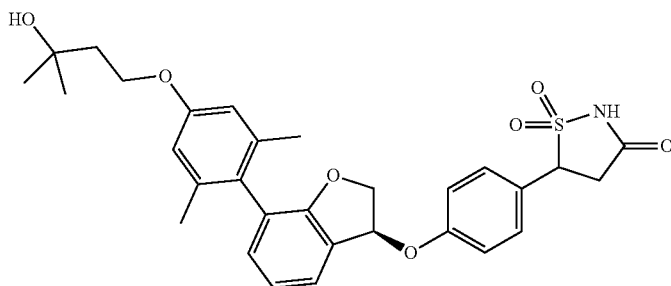


Structural Formula 15

Example 118P

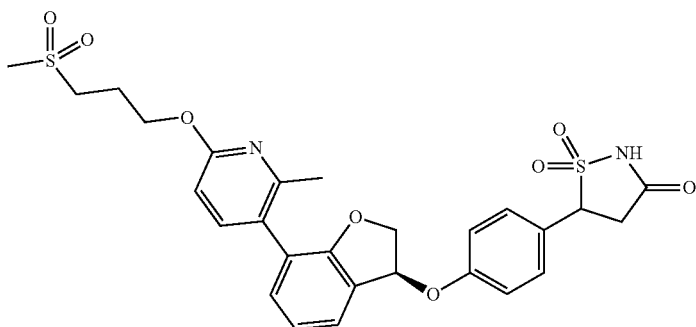


Example 119P

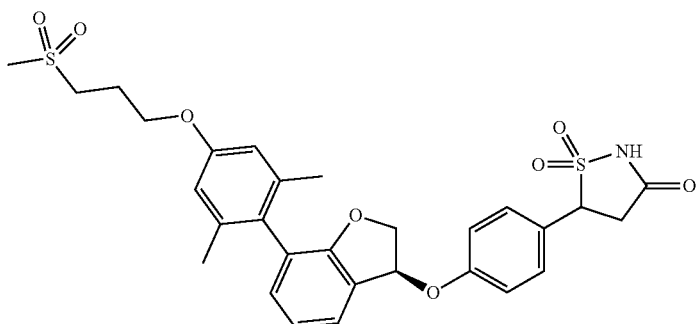


-continued

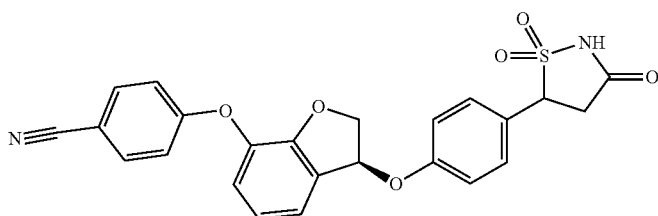
Example 120P



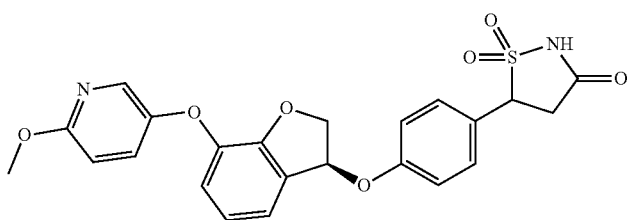
Example 121P



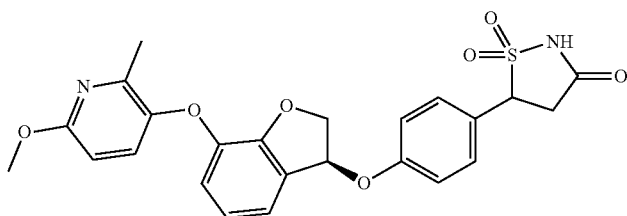
Example 122P



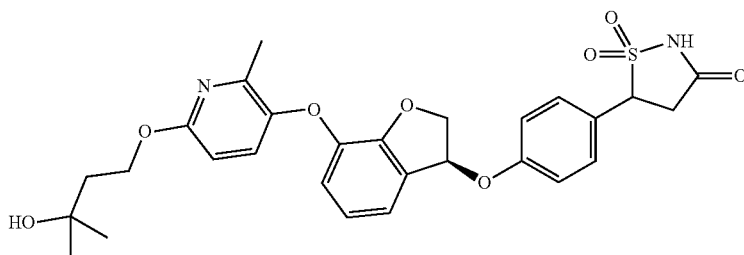
Example 123P



Example 124P



Example 125P

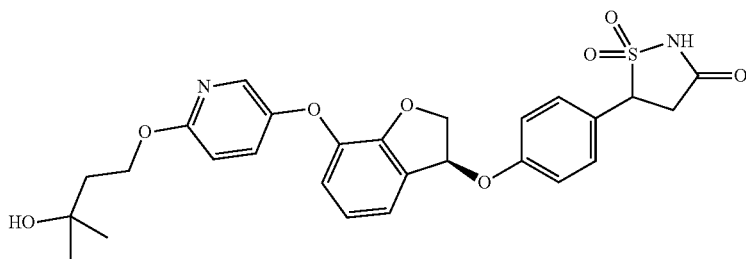


353

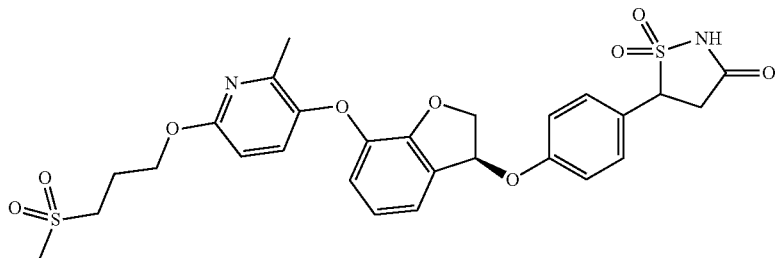
354

-continued

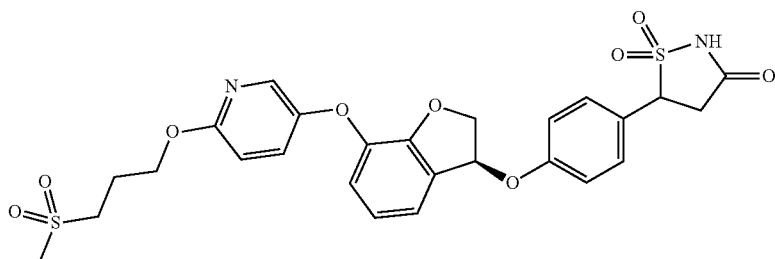
Example 126P



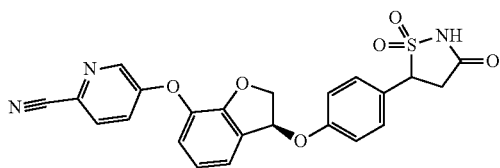
Example 127P



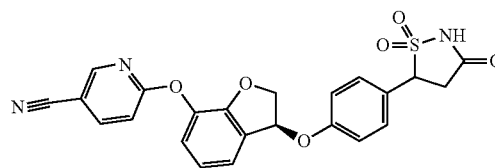
Example 128P



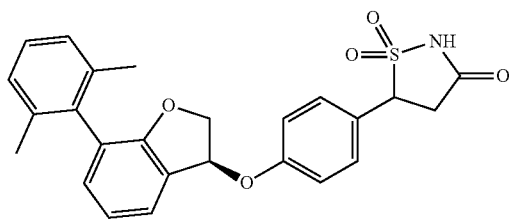
Example 129P



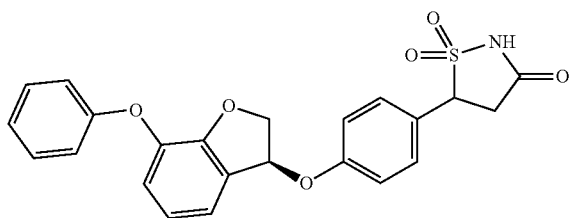
Example 130P



Example 131P

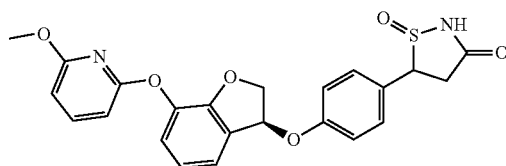


Example 132P

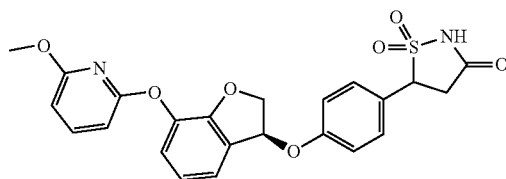


Structural Formula 16

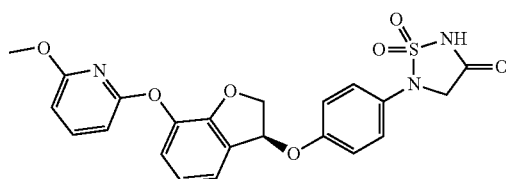
Example 134P



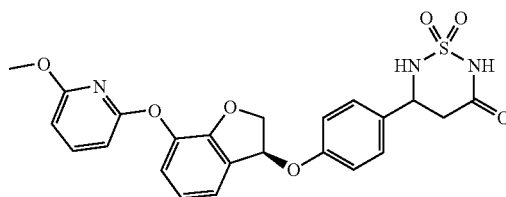
Example 136P



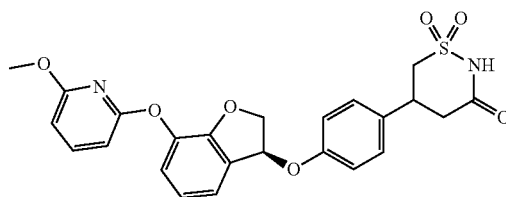
Example 138P



Example 140P

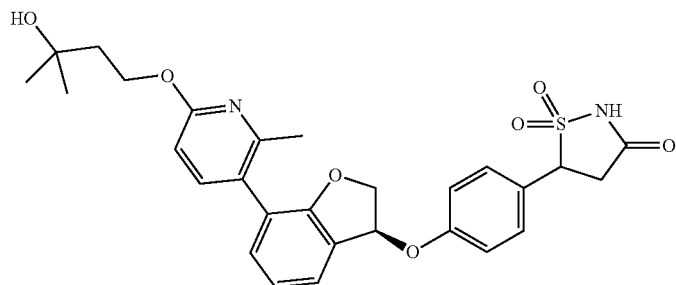


Example 142P



Structural Formula 17

Example 143P

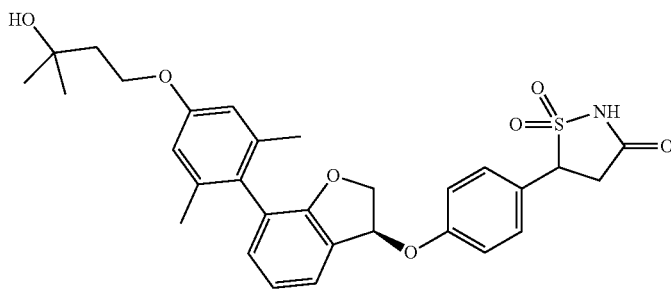


357

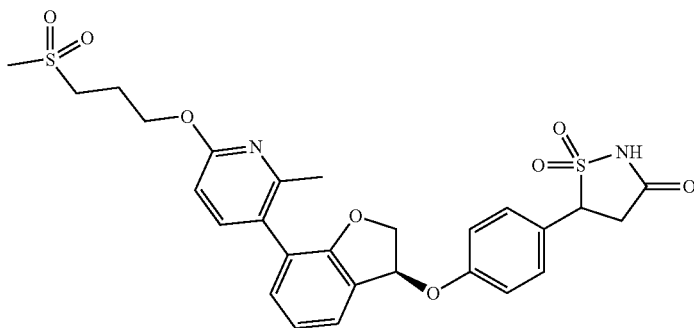
358

-continued

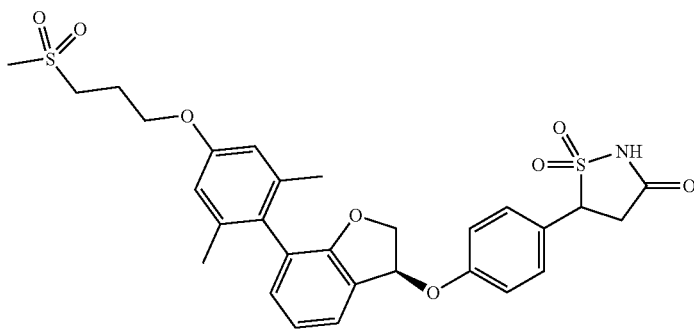
Example 144P



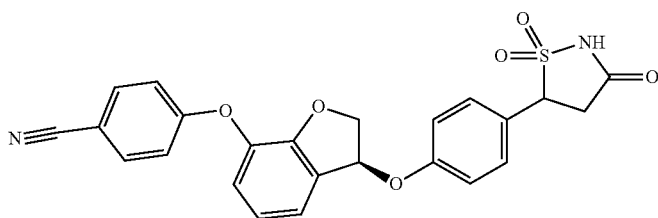
Example 145P



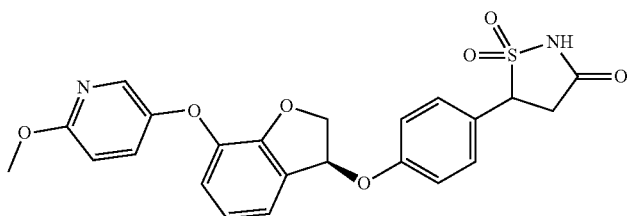
Example 146P



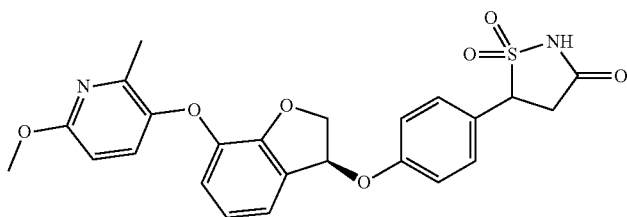
Example 147P



Example 148P



Example 149P

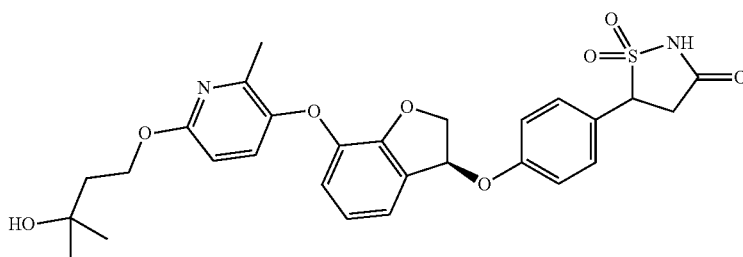


359

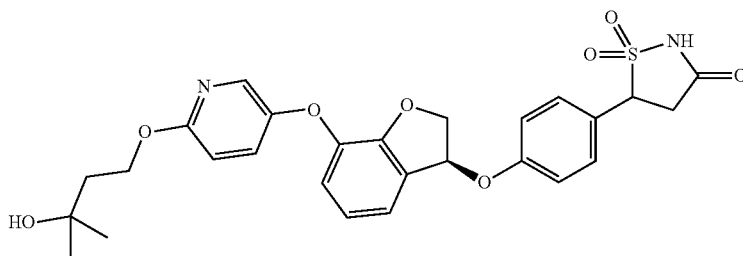
360

-continued

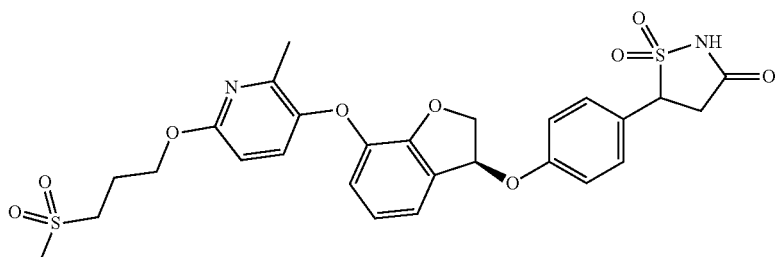
Example 150P



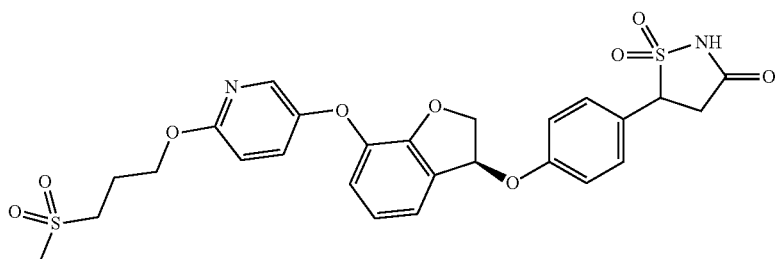
Example 151P



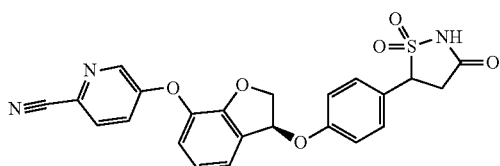
Example 152P



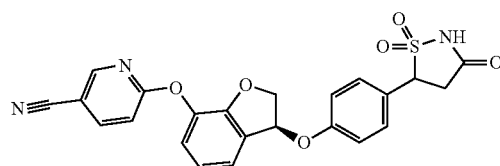
Example 153P



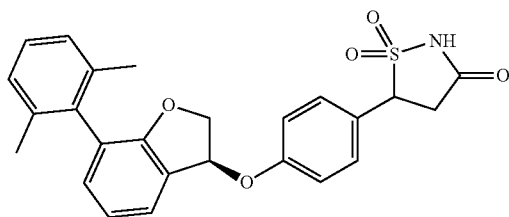
Example 154P



Example 155P

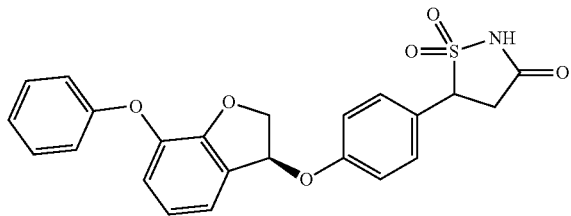


Example 156P



-continued

Example 157P



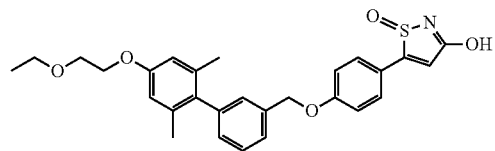
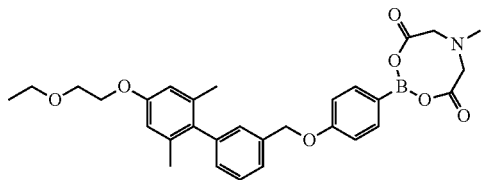
Structural Formula 18

Ex-
am-
ple
No.

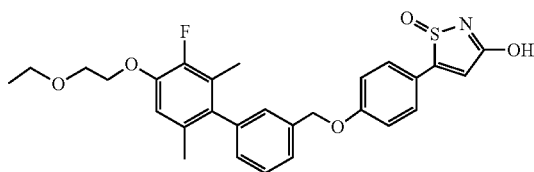
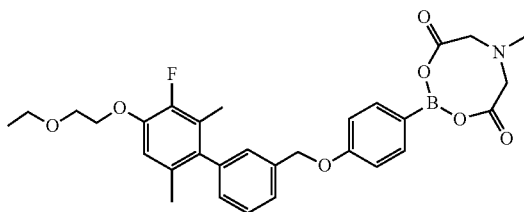
Substituted Phenylboronic Ester

Substituted Isothiazole

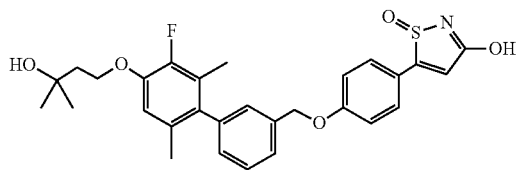
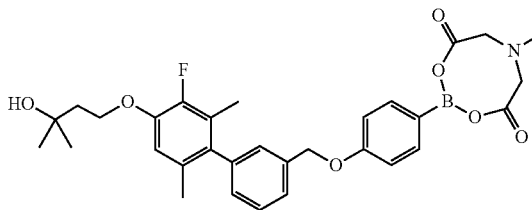
1



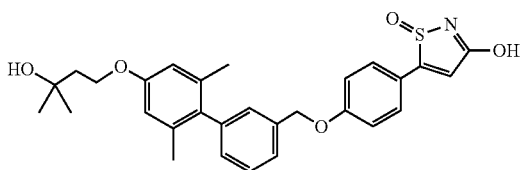
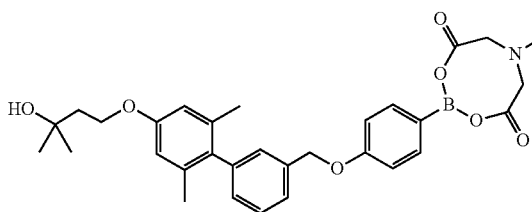
2



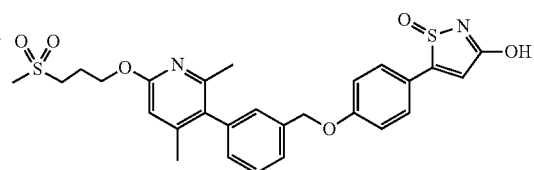
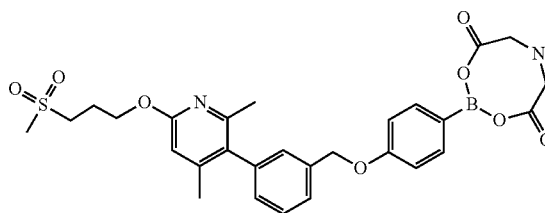
3



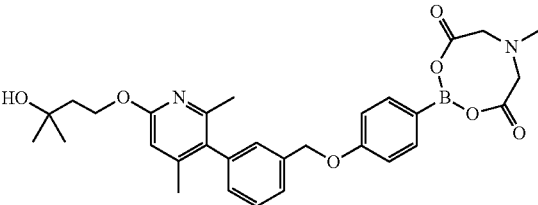
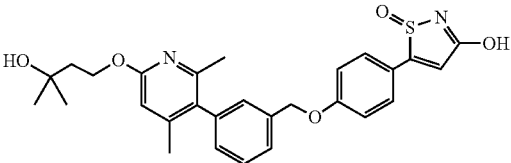
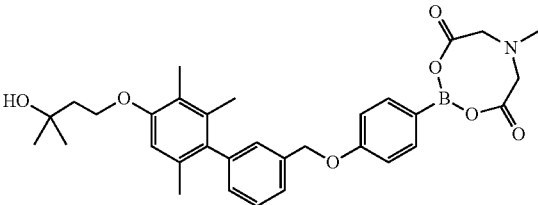
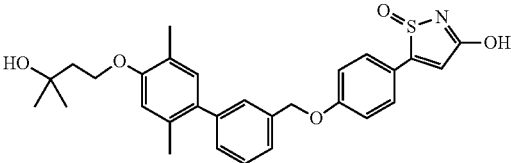
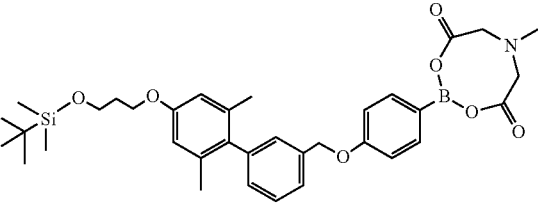
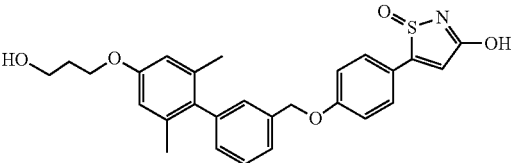
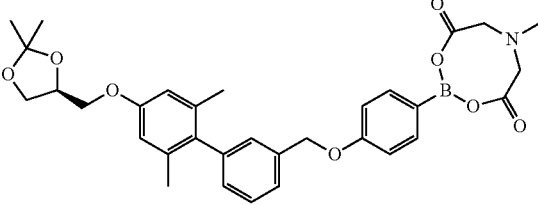
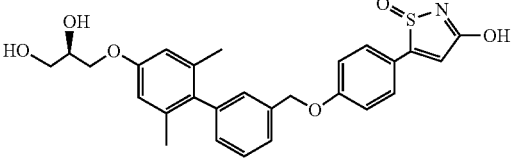
4



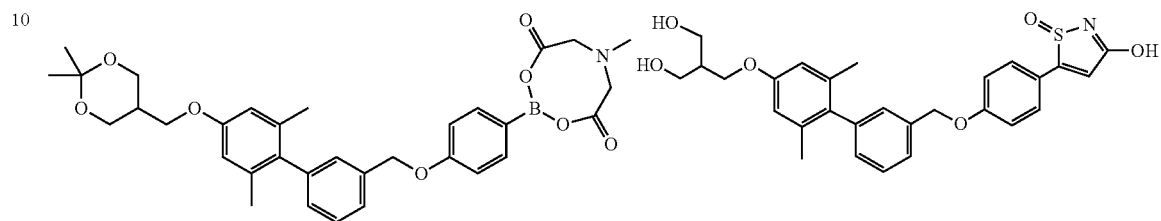
5



-continued

Structural Formula 18		
Ex- am- ple No.	Substituted Phenylboronic Ester	Substituted Isothiazole
6		
7		
8		
9		

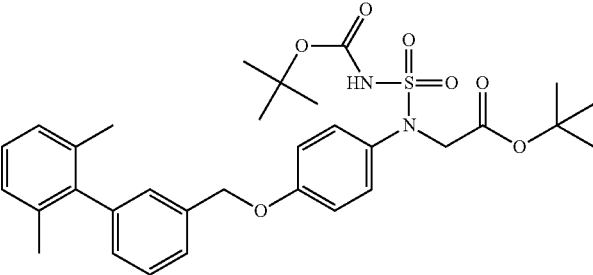
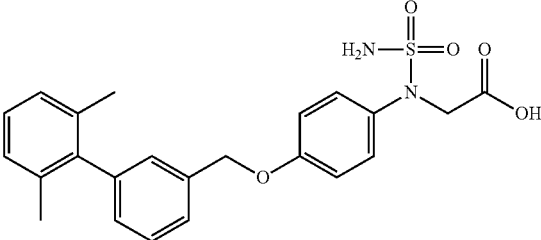
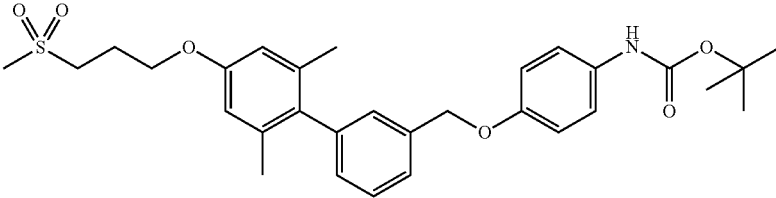
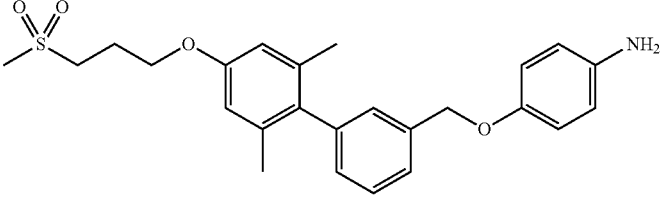
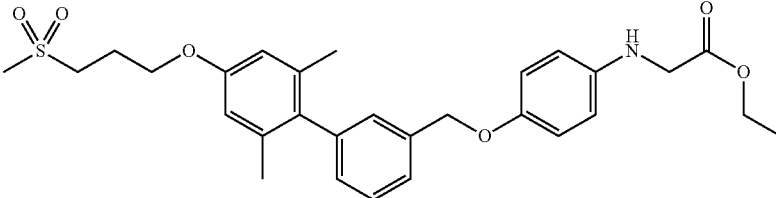
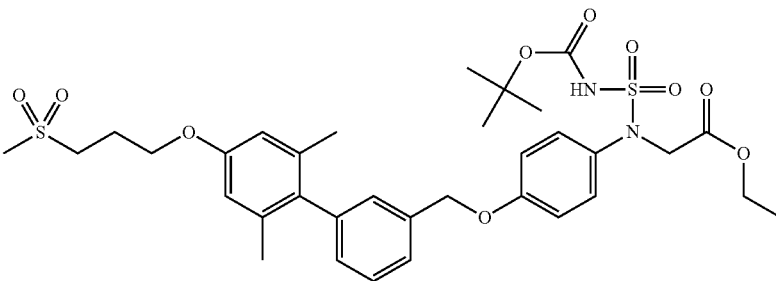
Structural Formula 19		
Ex- am- ple No.	Substituted Phenylboronic Ester	Substituted Isothiazole



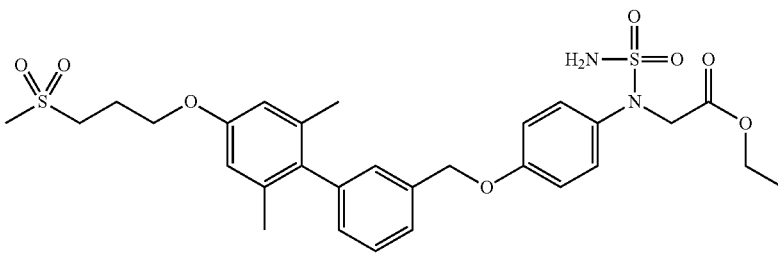
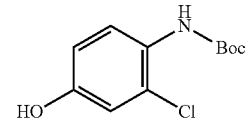
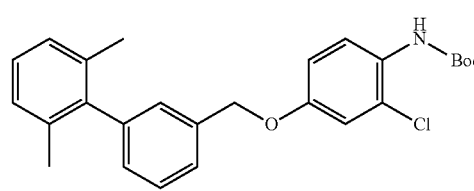
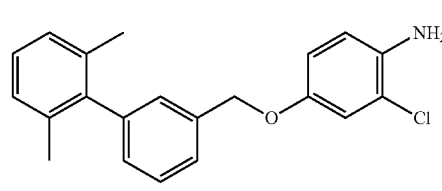
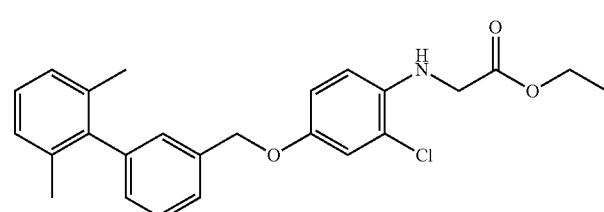
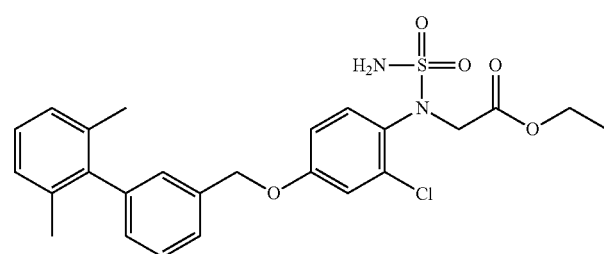
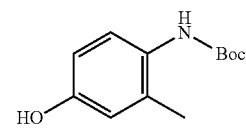
Ex- am- ple No.	Substituted Phenylboronic Ester	Substituted Isothiazole
11		
12		
13		

No.	Structure
14-1	
14-2	
14-3	

-continued

Structural Formula 20	
No.	Structure
14-4	
14-5	
15-1	
15-2	
15-3	
15-4	

-continued

Structural Formula 20	
No.	Structure
15-5	
16-1	
16-2	
16-3	
16-4	
16-5	
17-1	

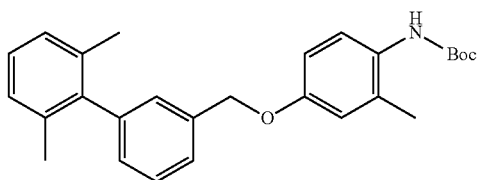
-continued

Structural Formula 20

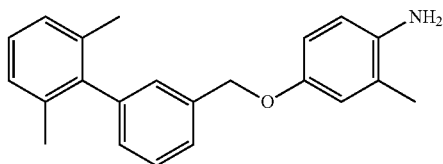
No.

Structure

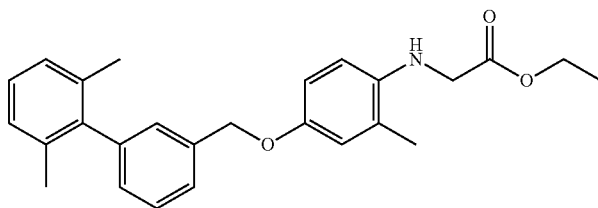
17-2



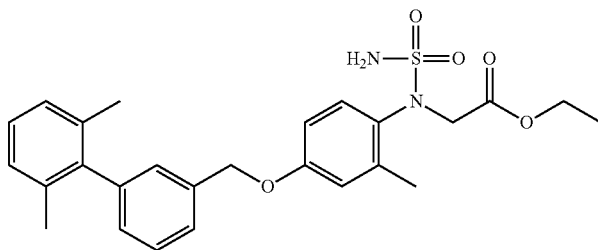
17-3



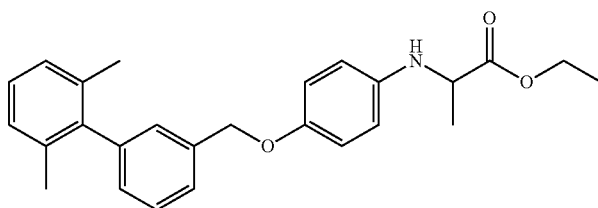
17-4



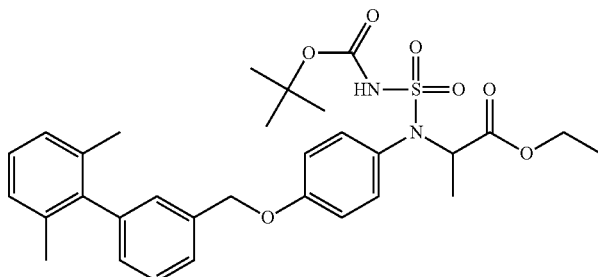
17-5



18-1



18-2

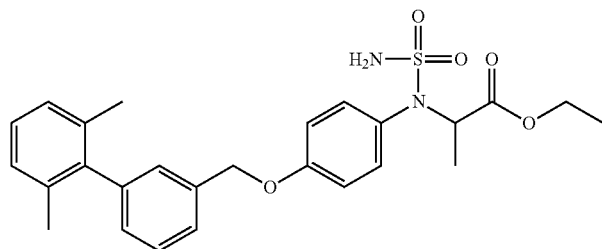


Structural Formula 21

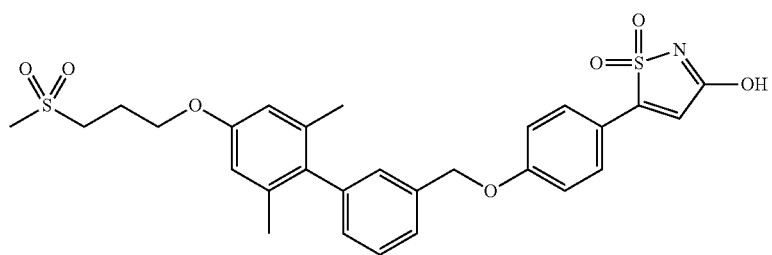
No.

Structure

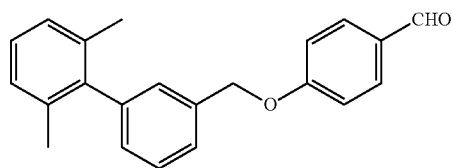
18-3



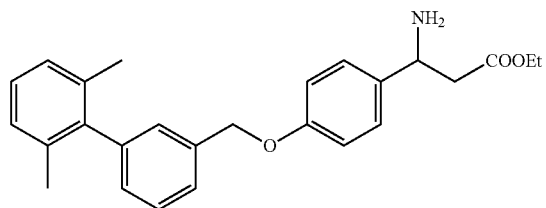
19-1



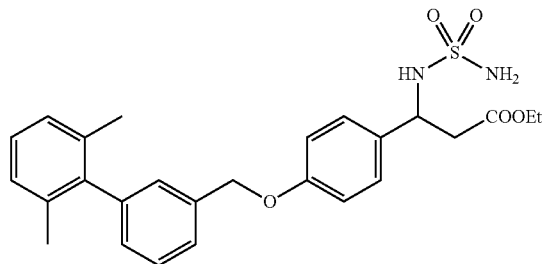
21-1



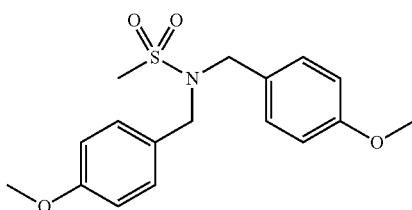
21-2

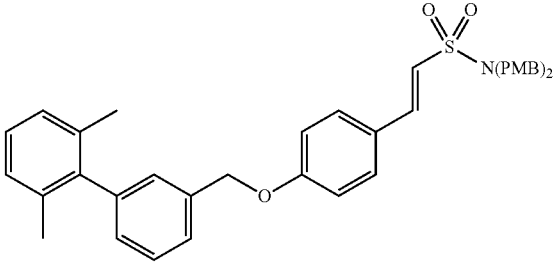
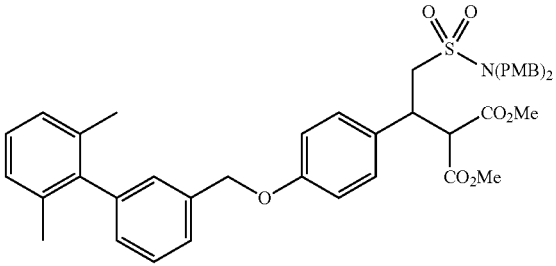
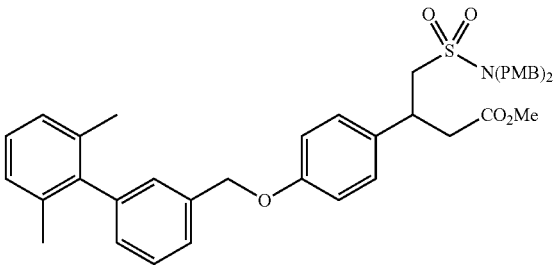
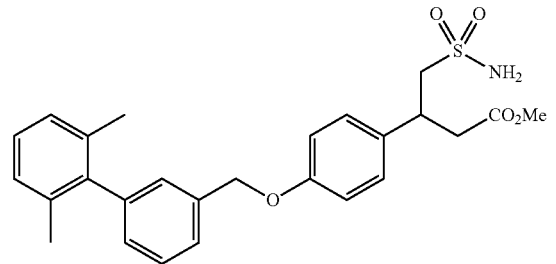


21-3

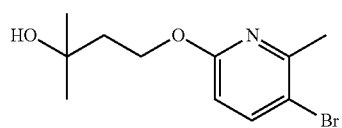


22-1

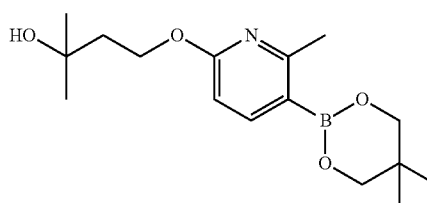


Structural Formula 21	
No.	Structure
22-2	
22-3	
22-4	
22-5	

Structural Formula 22



Example 23-1



Example 23-2

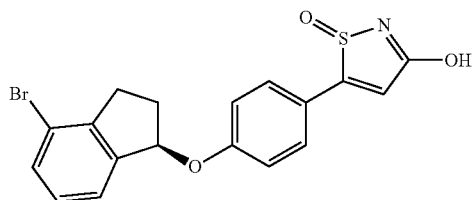
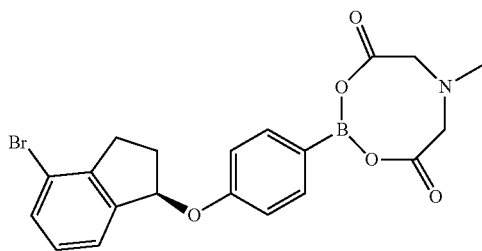
377

378

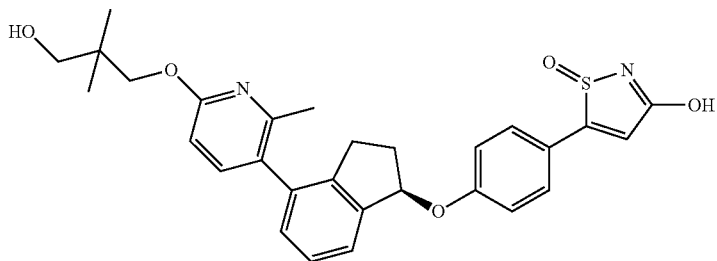
-continued

Example 23-3

Example 23-4

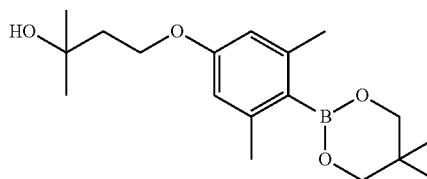
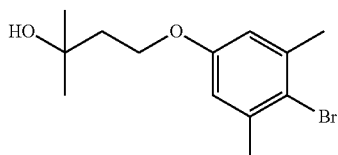


Example 23-5

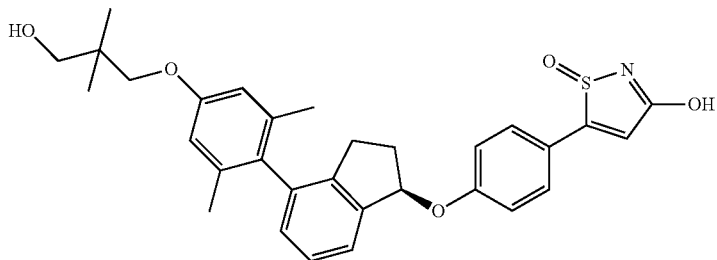


Example 24-1

Example 24-2

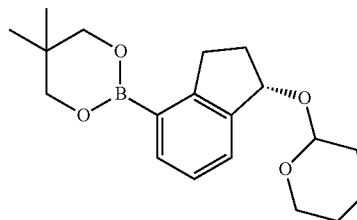
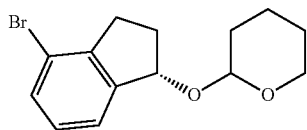


Example 24-3



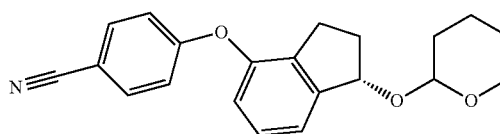
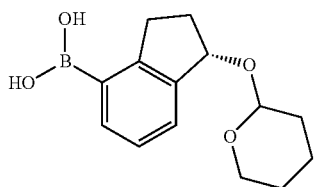
Example 25-1

Example 25-2

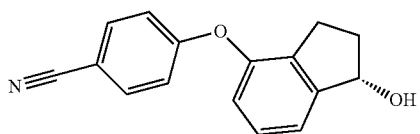


Example 25-3

Example 25-4



Example 25-5

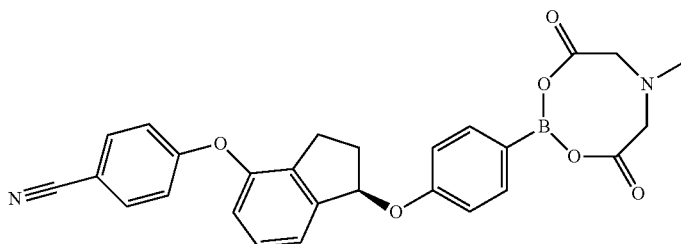


379

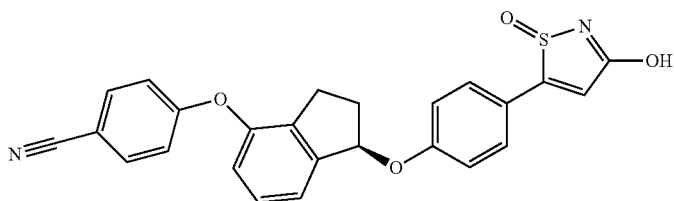
380

-continued

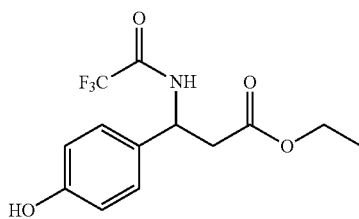
Example 25-6



Example 25-7

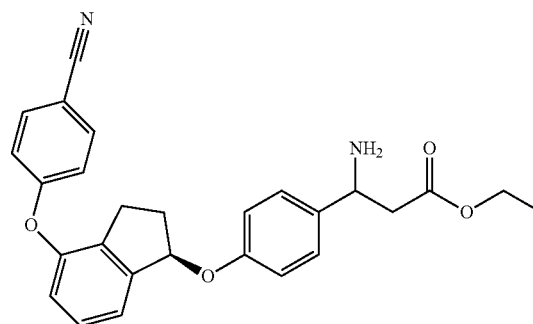
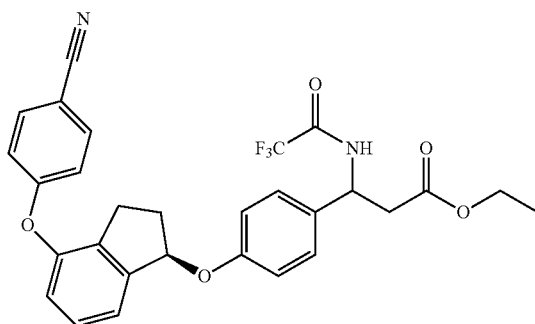


Example 26-1

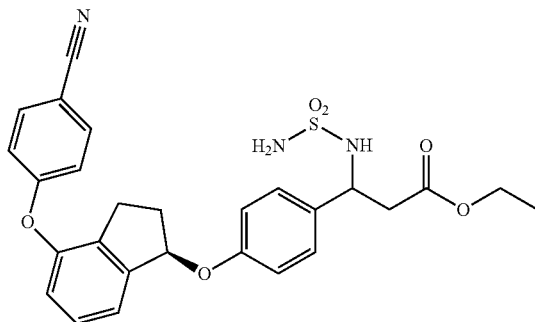


Example 26-2

Example 26-3



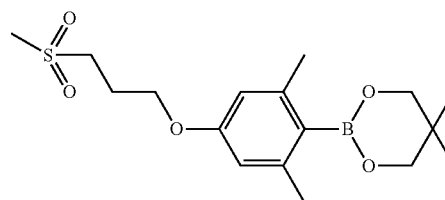
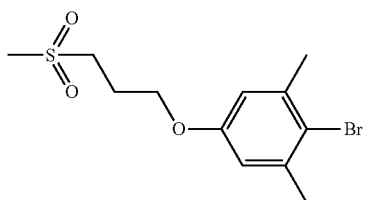
Example 26-4



Structural Formula 23

Example 30-1

Example 30-2

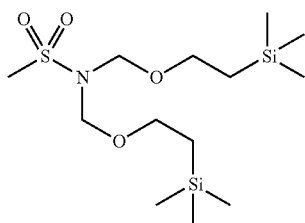


381

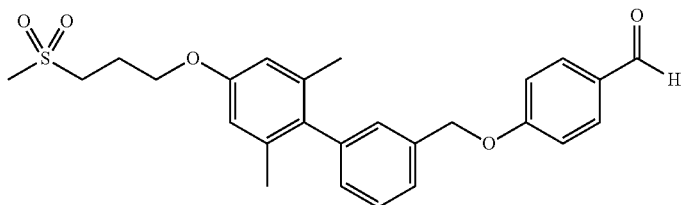
382

-continued

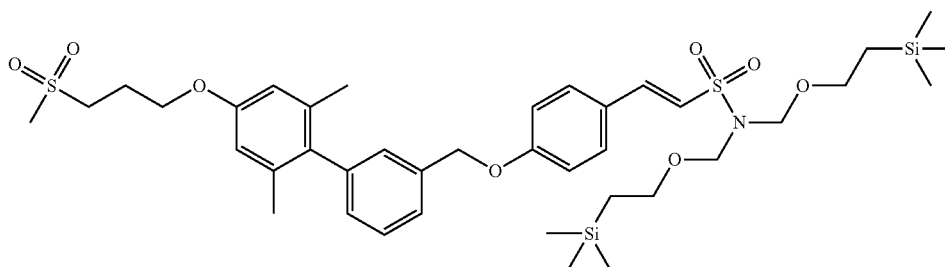
Example 31-3



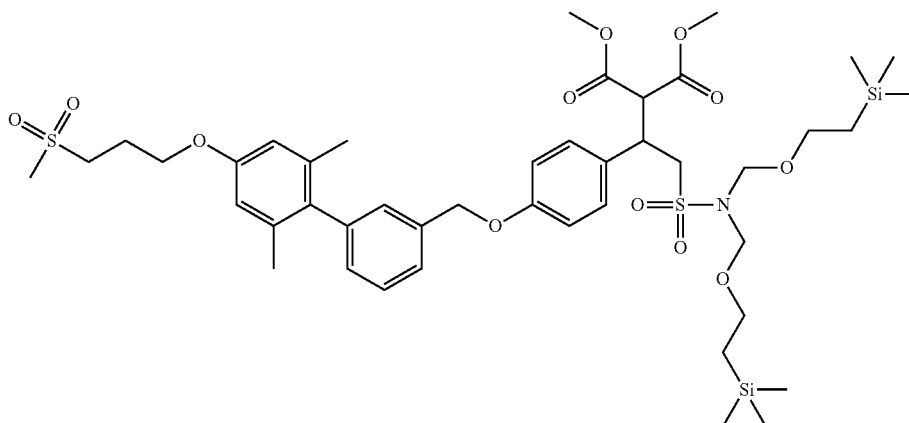
Example 31-2



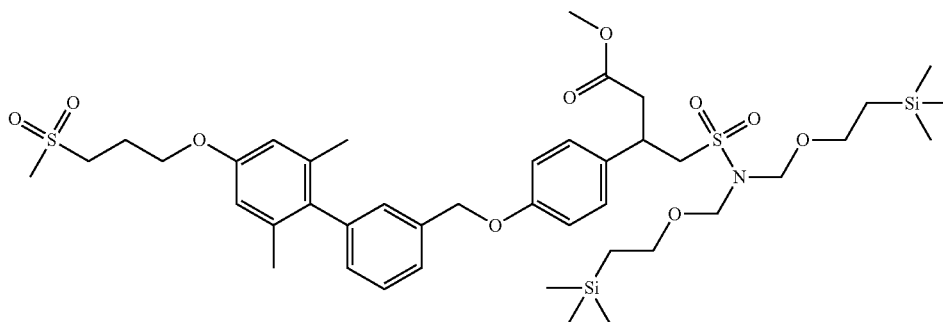
Example 31-3



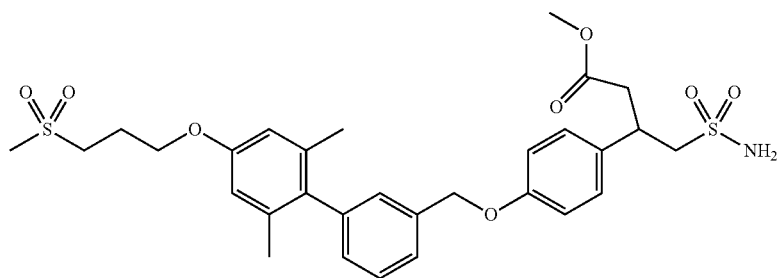
Example 31-4



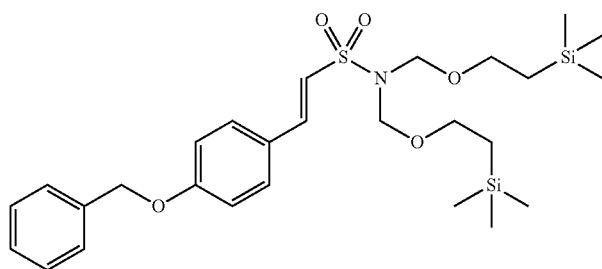
Example 31-5



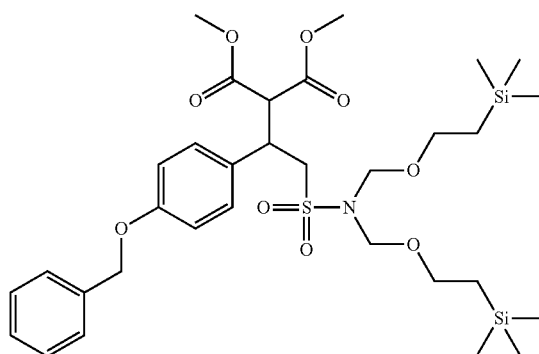
Example 31-6



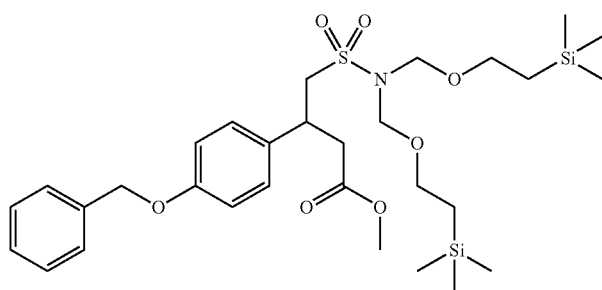
Example 32-1



Example 32-2

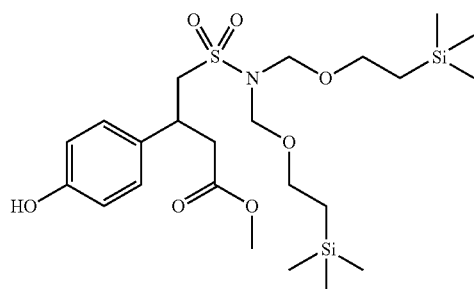


Example 32-3



Structural Formula 24

Example 32-4

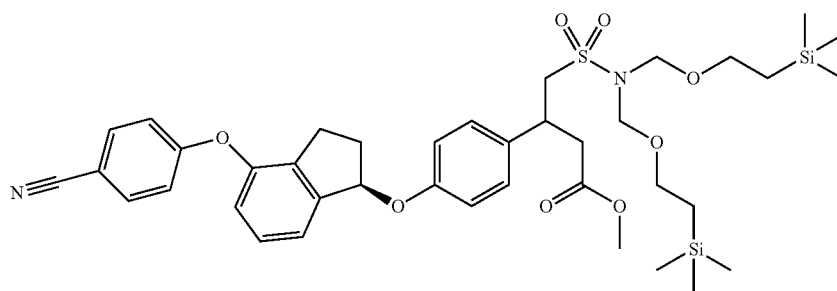


385

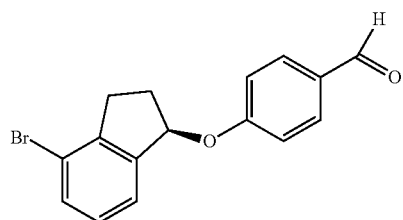
386

-continued

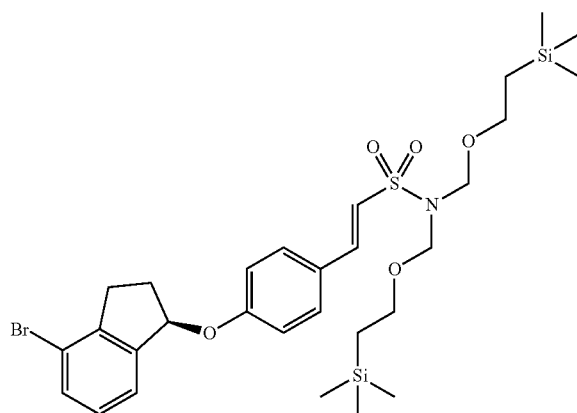
Example 32-5



Example 33-1

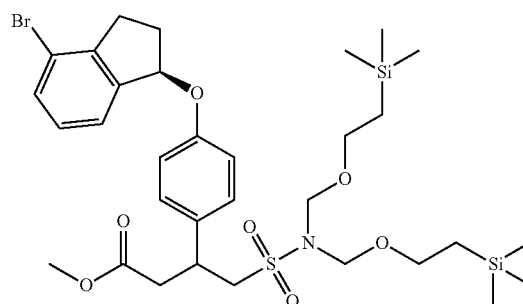
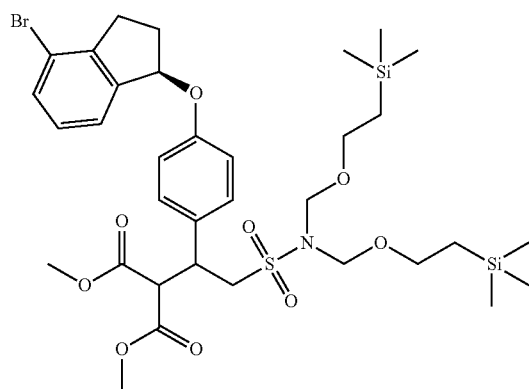


Example 33-2

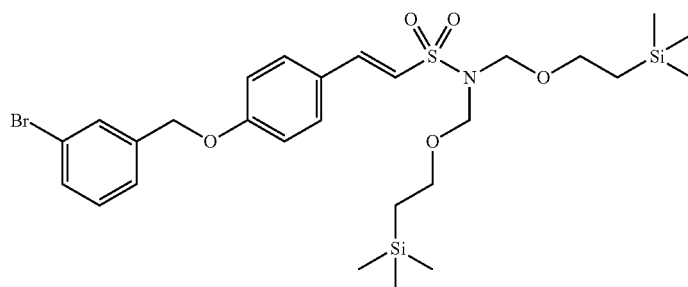


Example 33-3

Example 33-4



Example 35-1

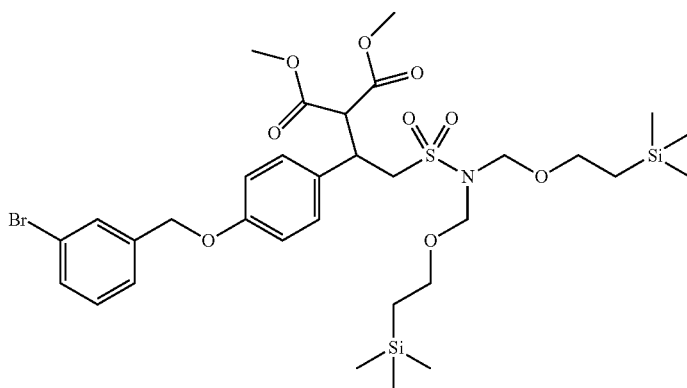


387

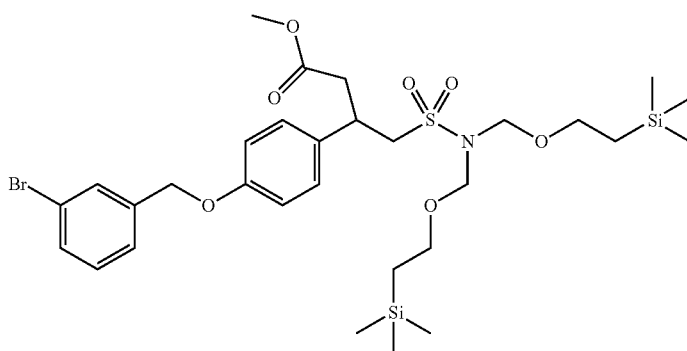
388

-continued

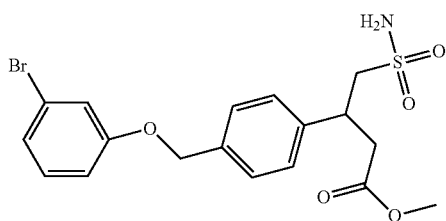
Example 35-2



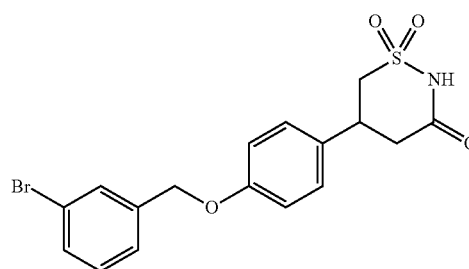
Example 35-3



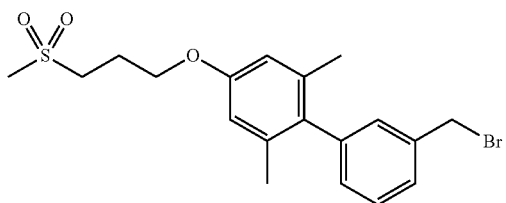
Example 35-4



Example 35-5

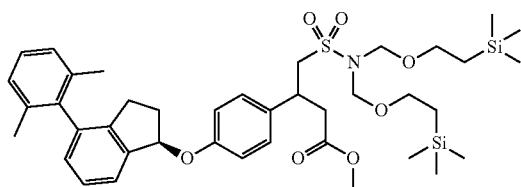


Reference Example 2

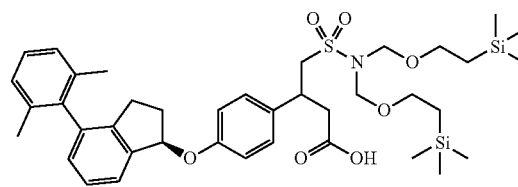


Structural Formula 25

Example 37-1



Example 37-2

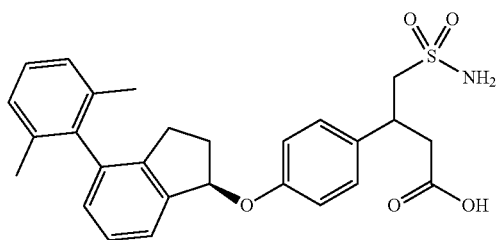


389

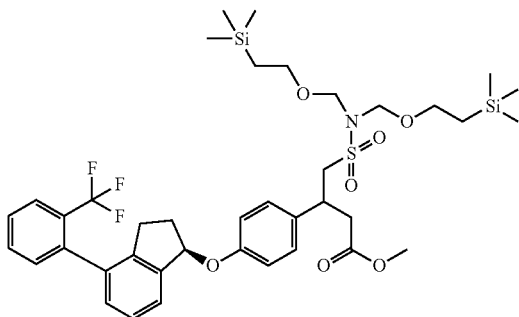
390

-continued

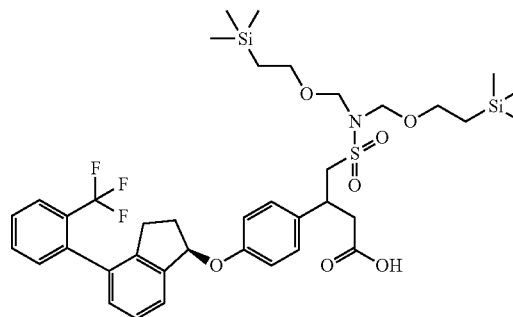
Example 37-3



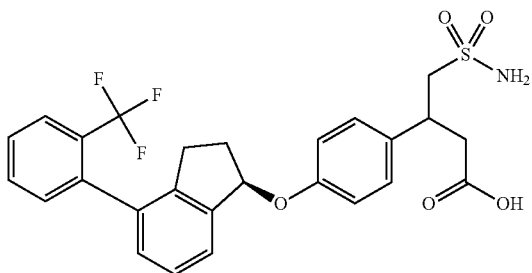
Example 38-1



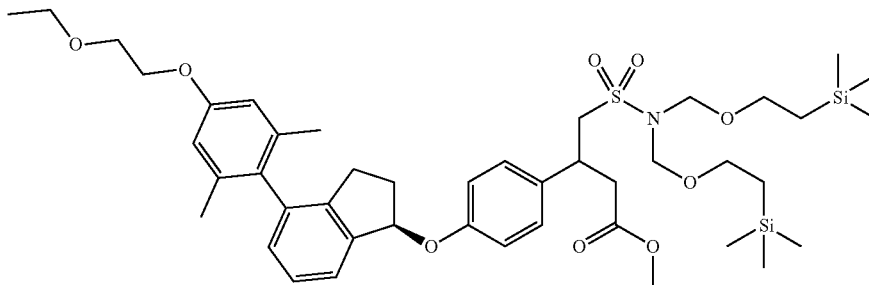
Example 38-2



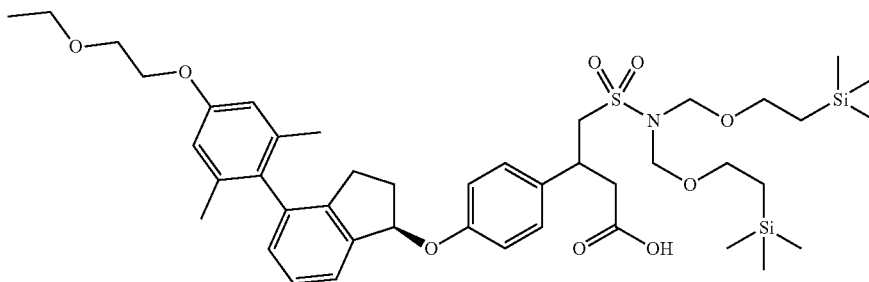
Example 38-3



Example 39-1



Example 39-2

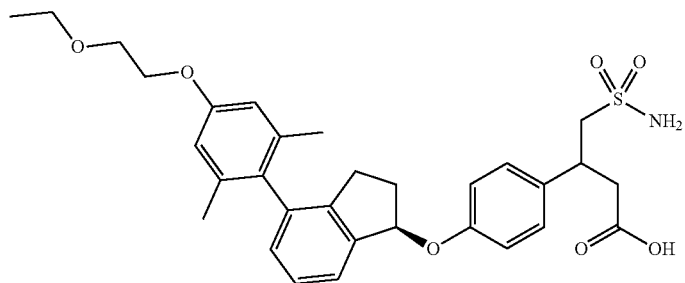


391

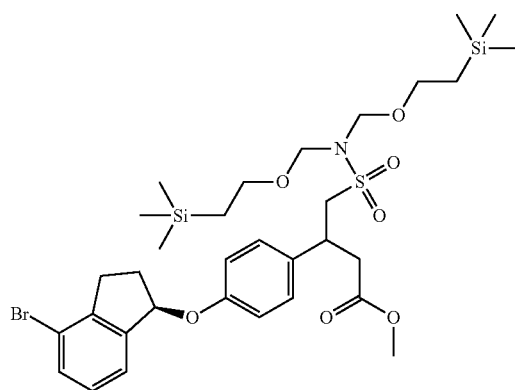
392

-continued

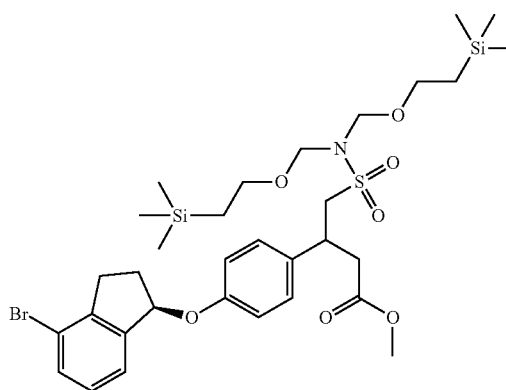
Example 39-3



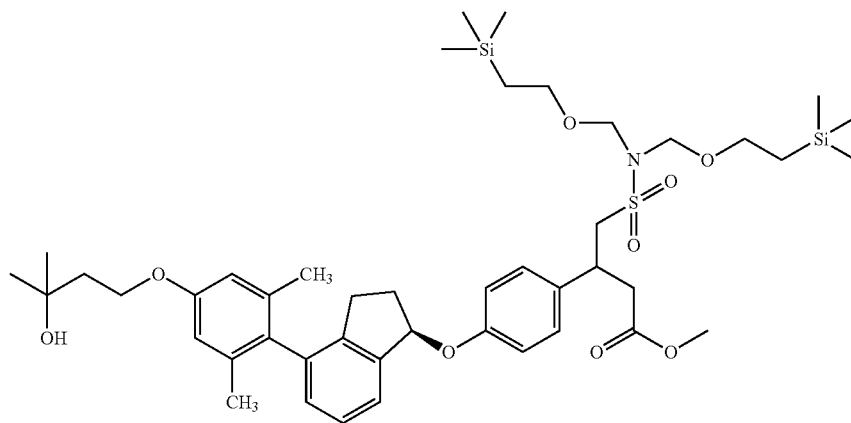
Example 40-1A



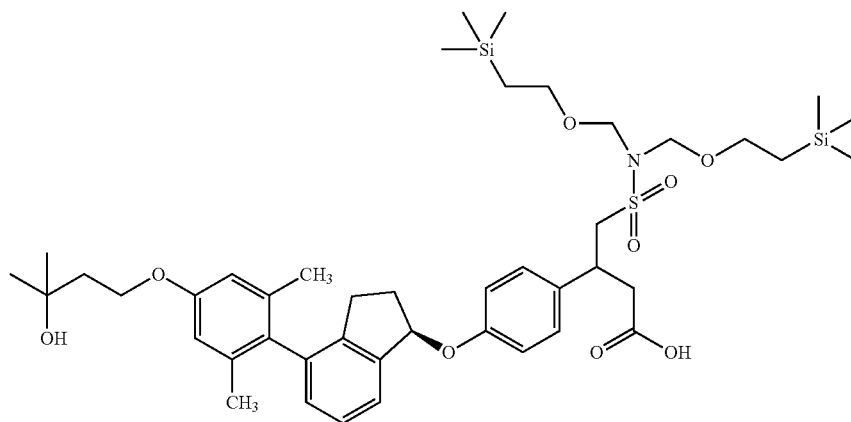
Example 40-1B



Example 40-2A



Example 40-3A

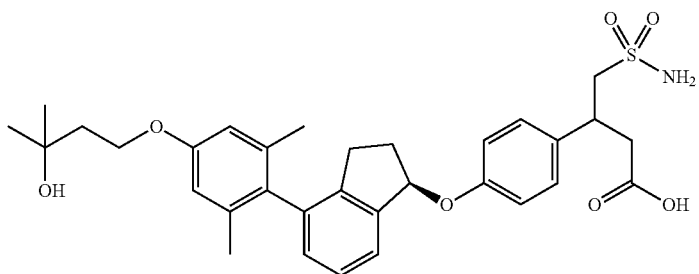


393

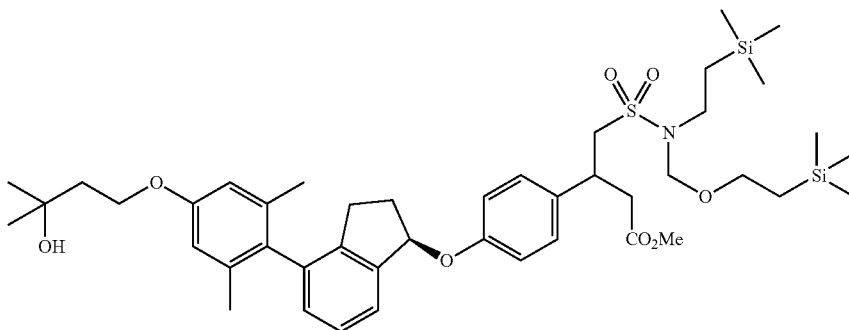
394

-continued

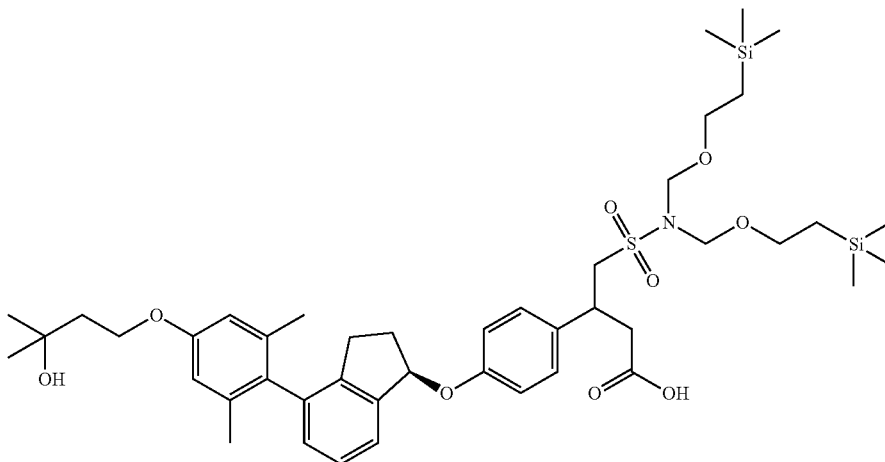
Example 40-4A



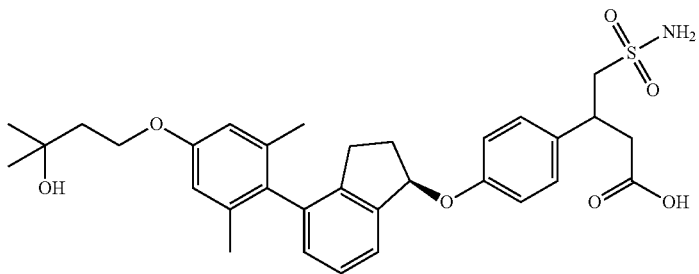
Example 41-1B



Example 41-2B



Example 41-3B



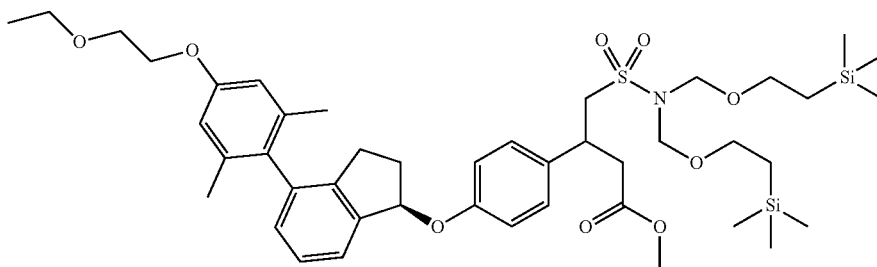
395

396

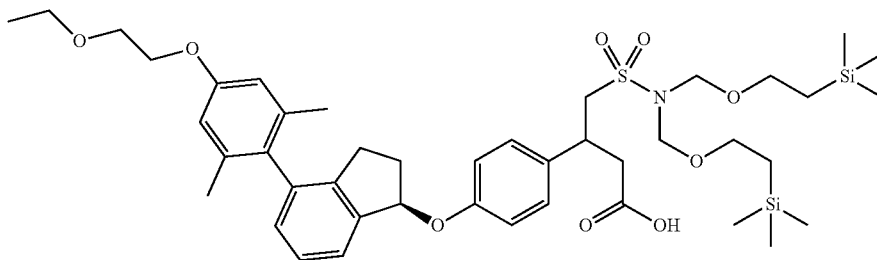
-continued

Structural Formula 26

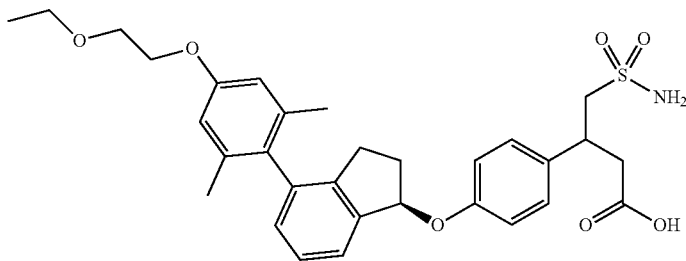
Example 42-1A



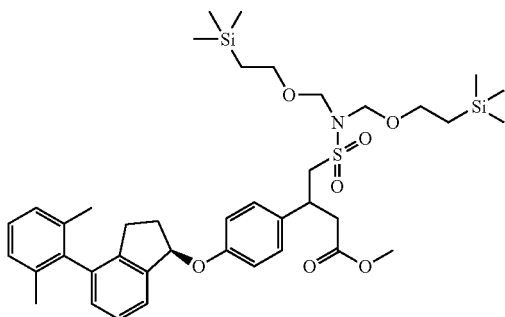
Example 42-2A



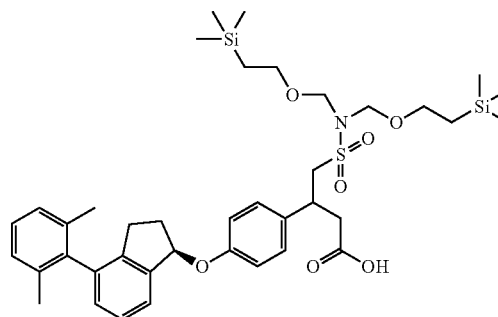
Example 42-3A



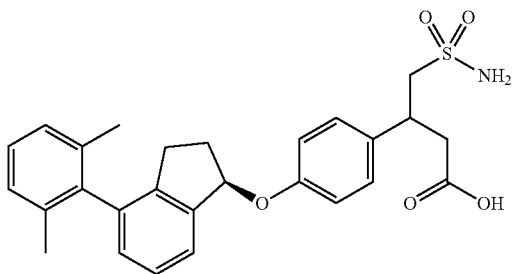
Example 43-1A



Example 43-2A



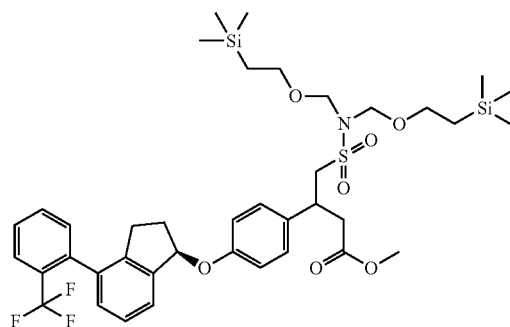
Example 43-3A



397

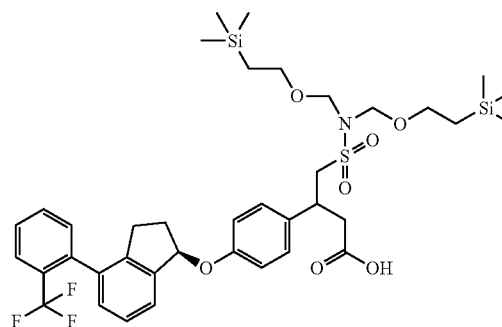
-continued

Example 44-1A

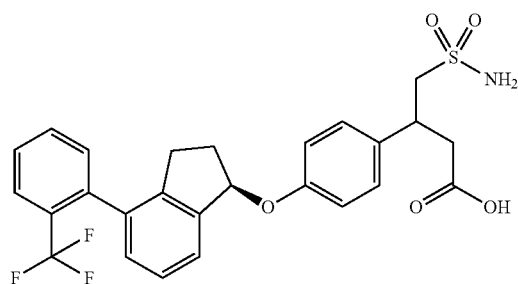


398

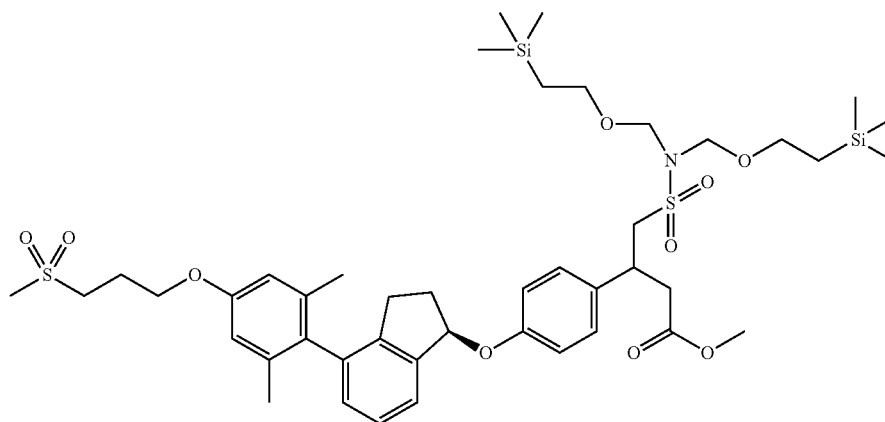
Example 44-2A



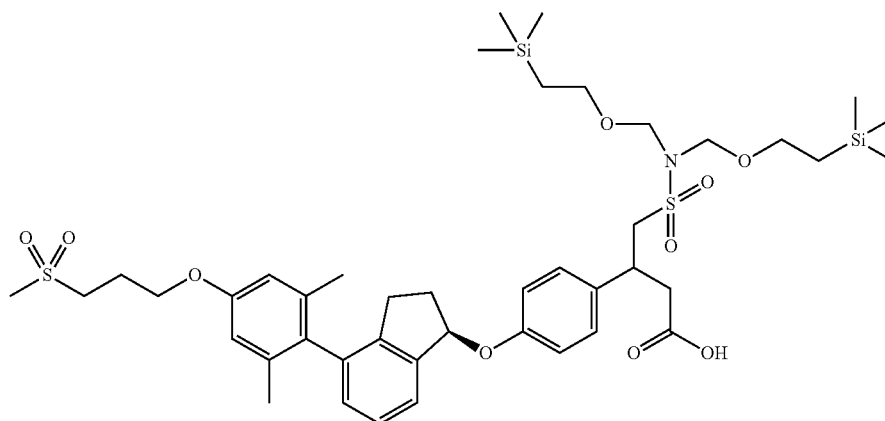
Example 44-3A



Example 45-1A

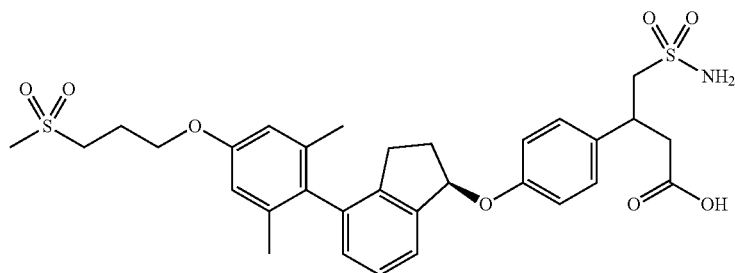


Example 45-2A

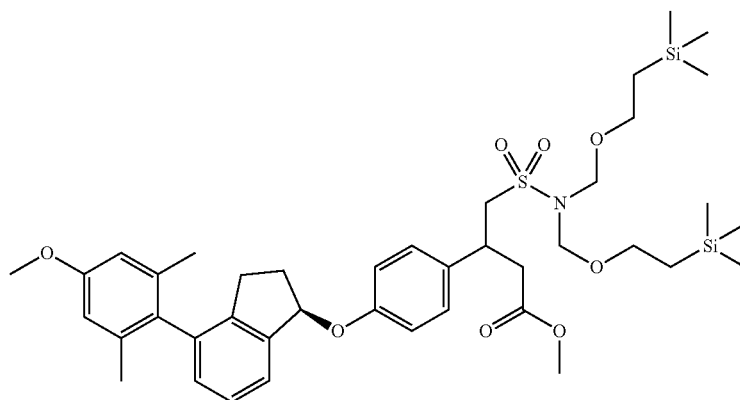


-continued

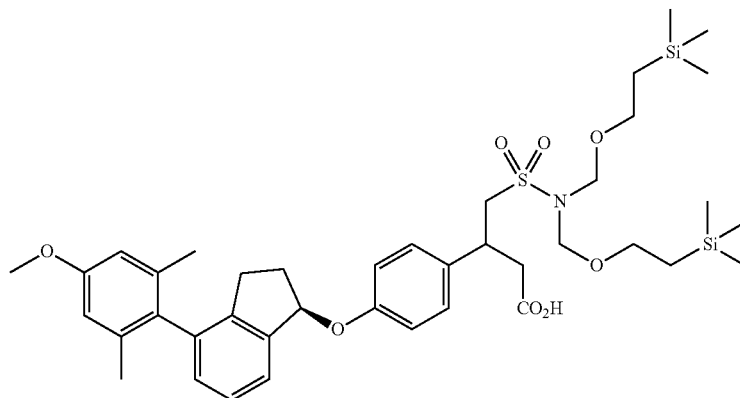
Example 45-3A



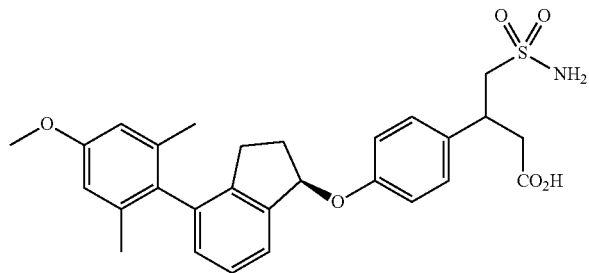
Example 46-1A



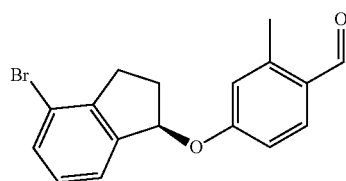
Example 46-2A



Example 46-3A



Example 47-1

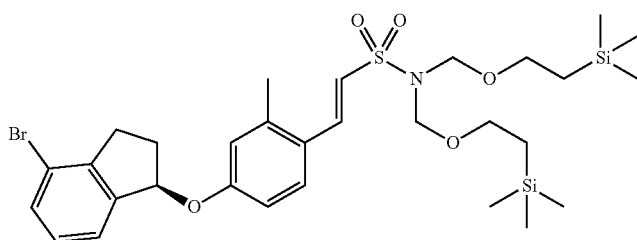


401

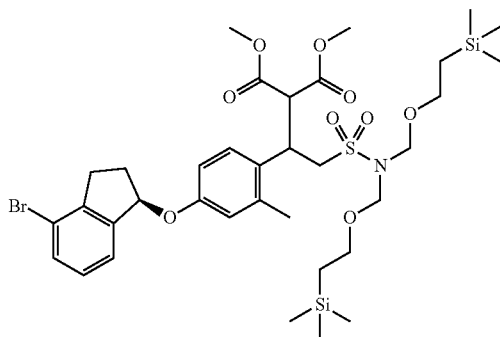
402

-continued

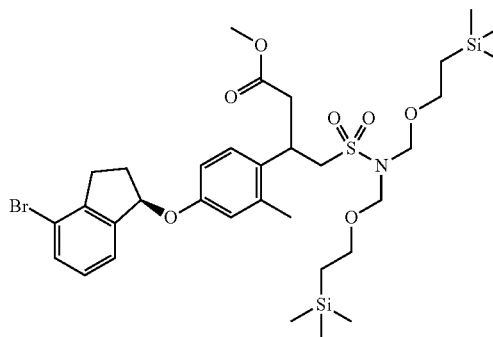
Example 47-2



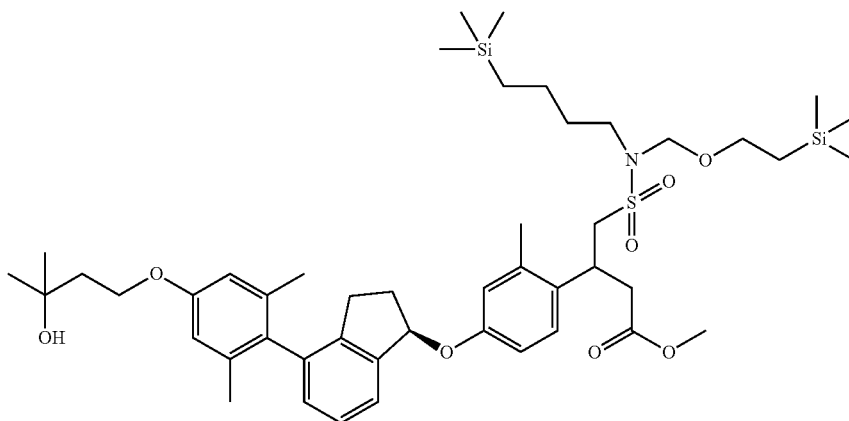
Example 47-3



Example 47-4

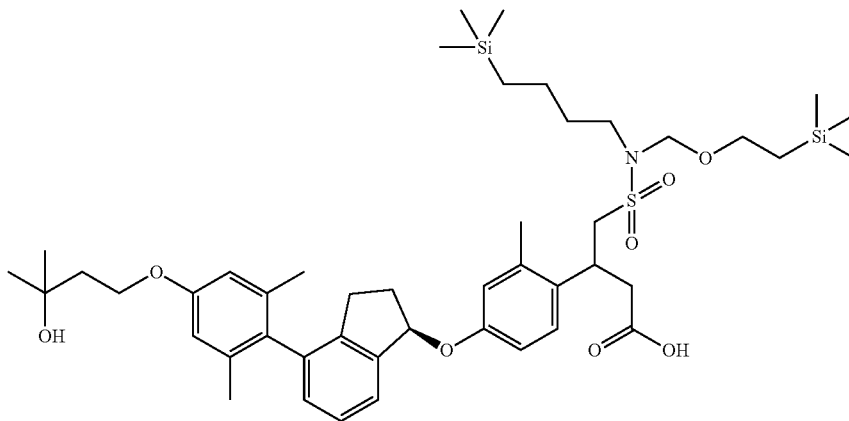


Example 47-5

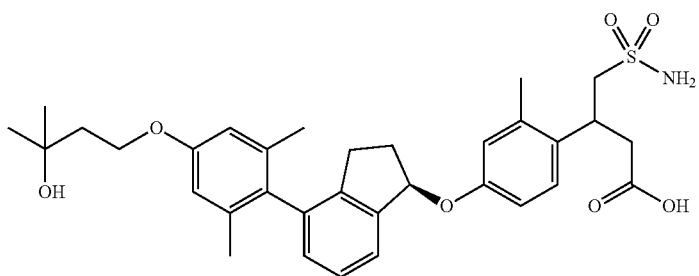


Structural Formula 27

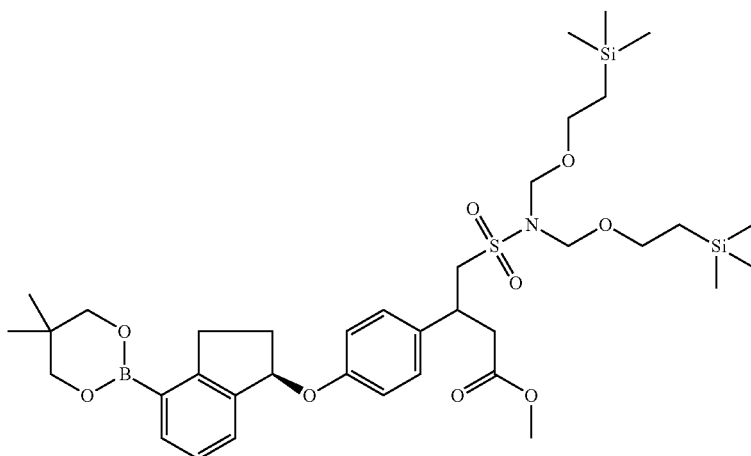
Example 47-6



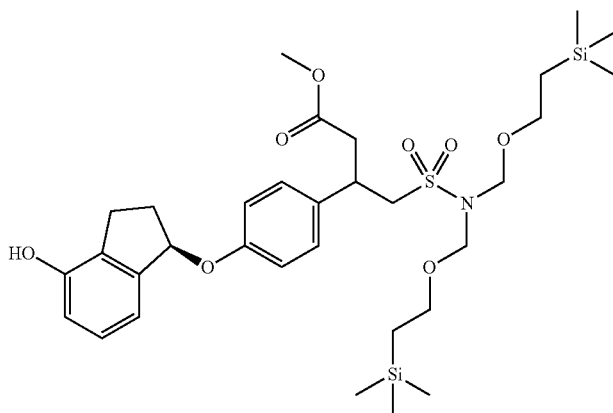
Example 47-7



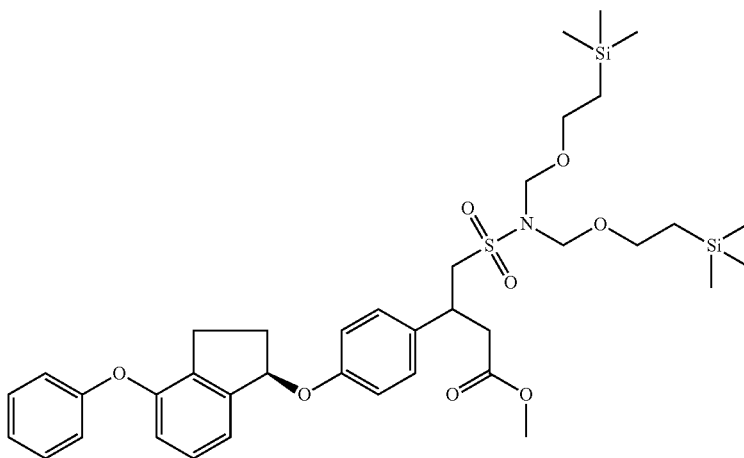
Example 48-1



Example 48-2



Example 48-3

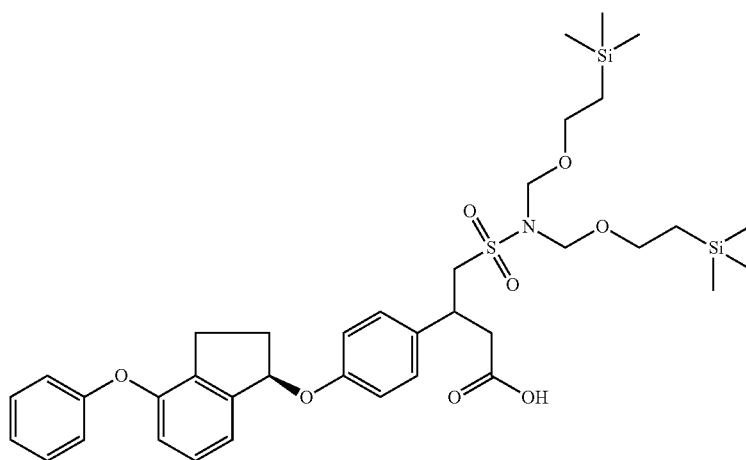


405

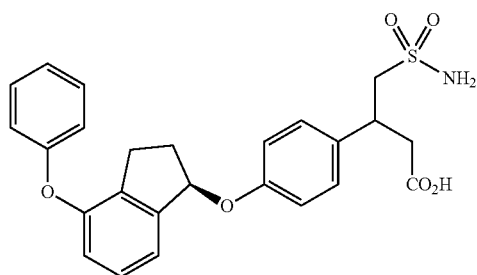
406

-continued

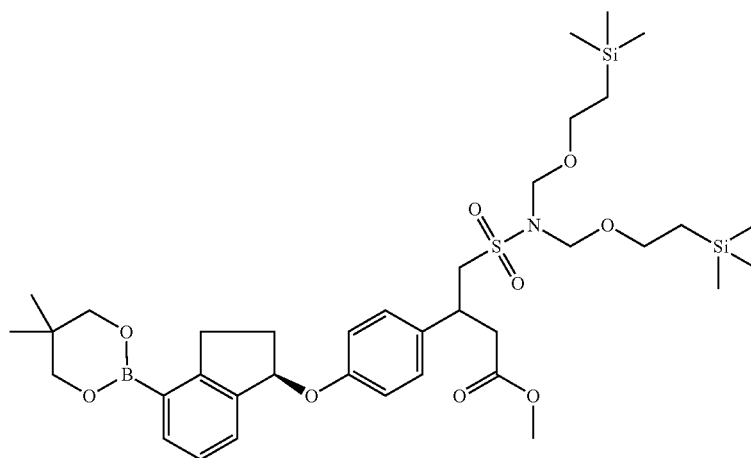
Example 48-4



Example 48-5



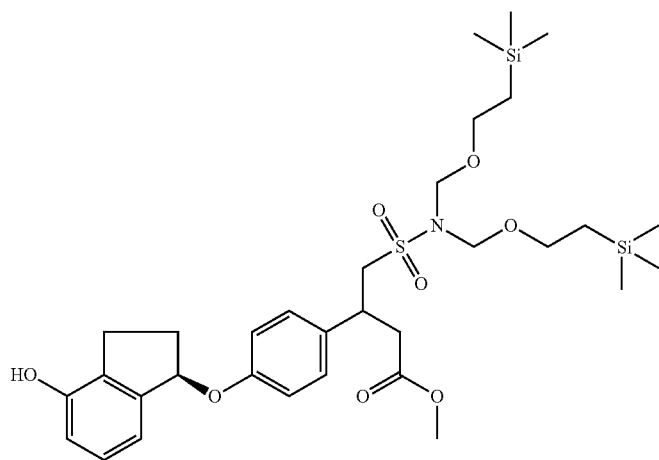
Example 49-1A



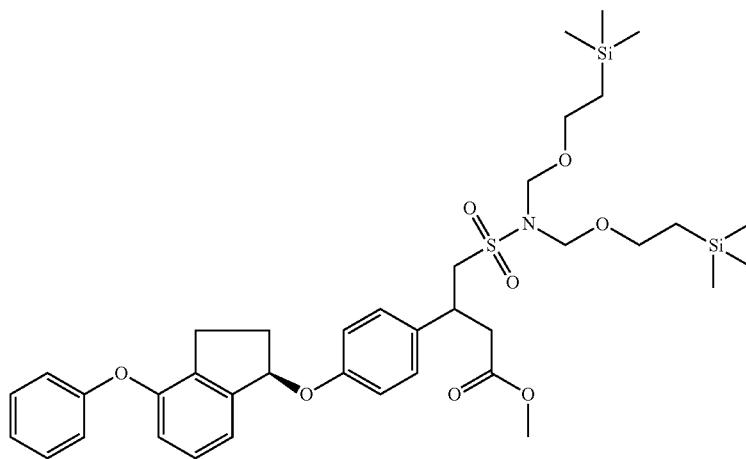
407

408

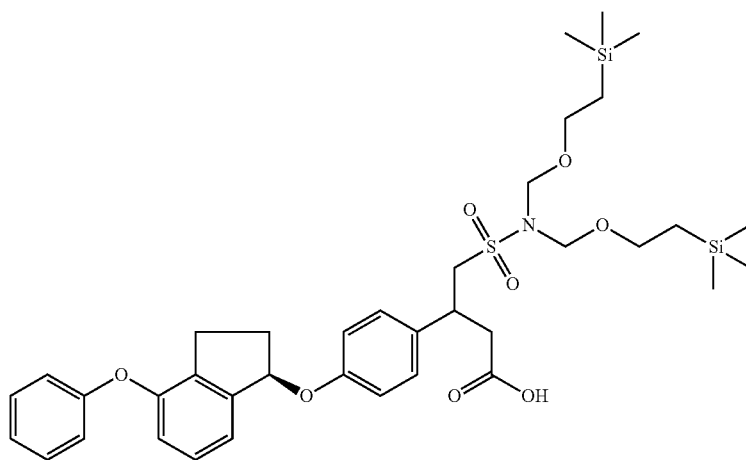
-continued



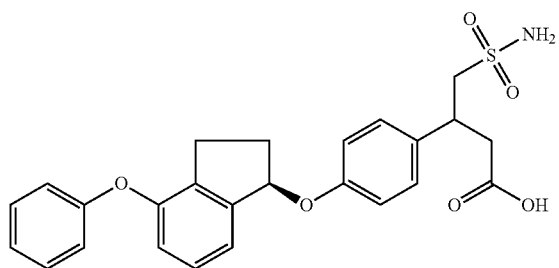
Example 49-2A



Example 49-3A

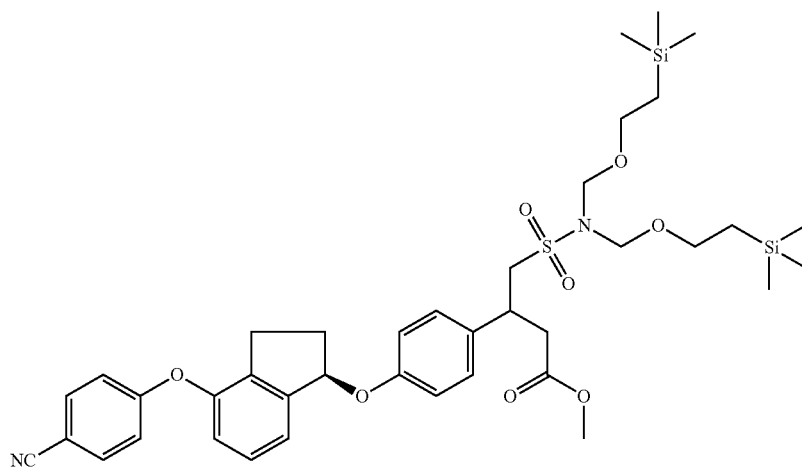


Example 49-4A

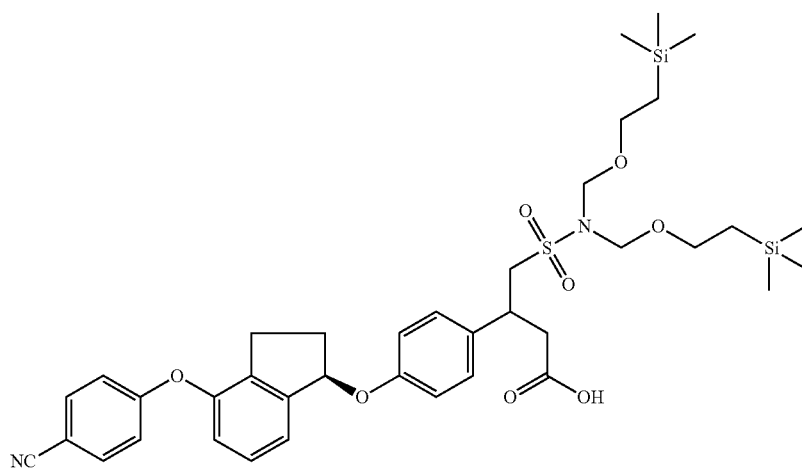


Example 49-5A

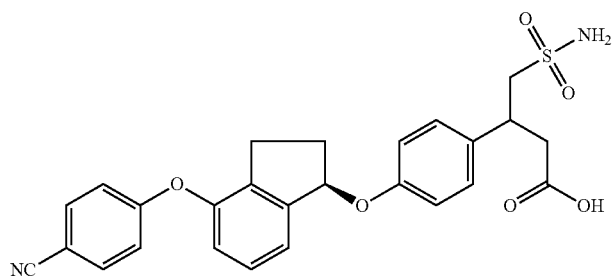
Example 50-1A



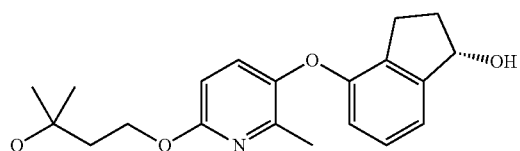
Example 50-2A



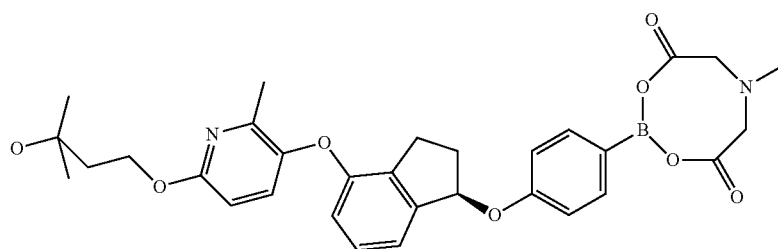
Example 50-3A



Example 51-1



Example 51-2

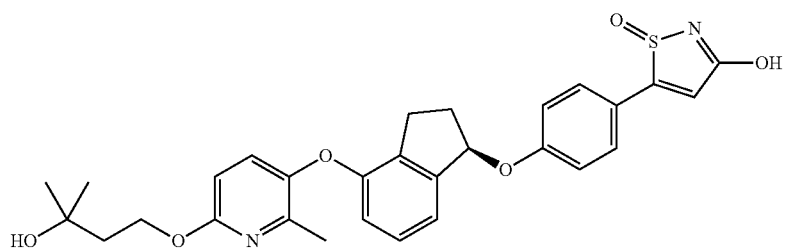


411

412

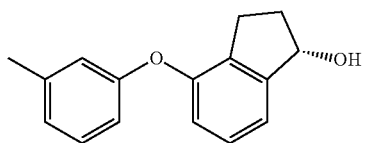
-continued

Example 51-3

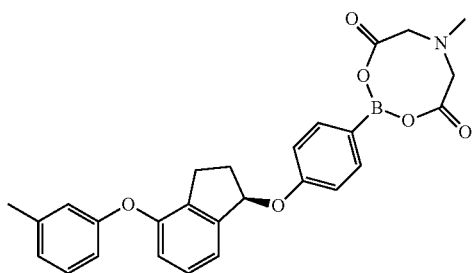


Structural Formula 28

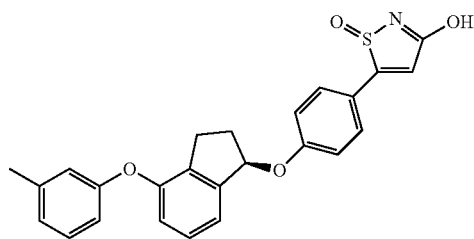
Example 53-1



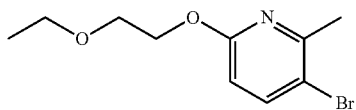
Example 53-2



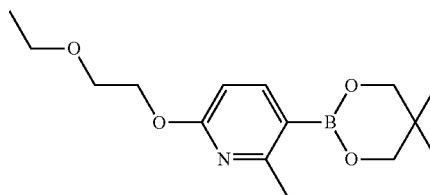
Example 53-3



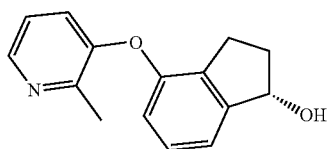
Example 54-1



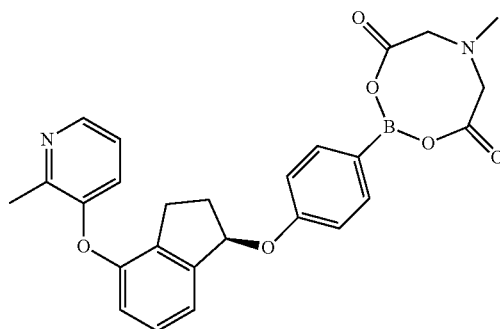
Example 54-2



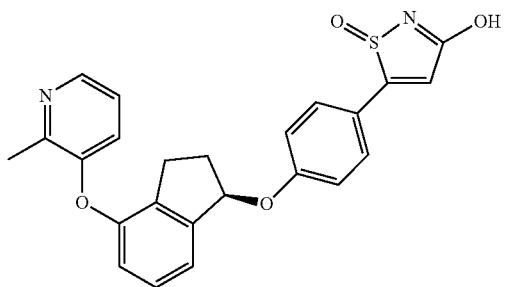
Example 55-1



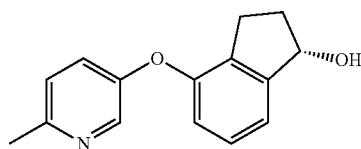
Example 55-2



Example 55-3



Example 52-1

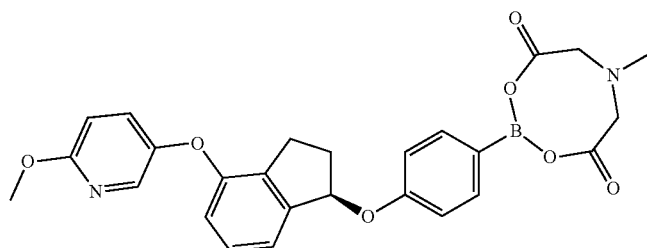


413

414

-continued

Example 52-2



Example 52-3

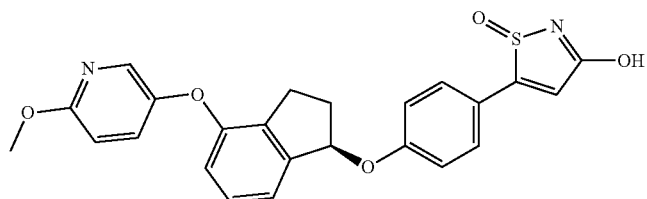


TABLE 2

Example No.	ESI-MS (M + 1) ⁺	Retention Time (Minute)
1	494	6.10
2	512	6.03
3	526	6.00
4	530*	5.98
5(A)-b	543	5.32
6(A)-b	509	5.77
7(A)-a	530*	6.20
8	480	5.79
9	496	5.33
10	510	5.42
11	479	3.90
12	494	5.97
13(A)-a	542	5.62
14	445*	5.72#
15	559	6.50
16	456&	—
17	436&	—
18	459*	5.65
19	558	5.82#
20	525	4.73#
21	437	6.20#
22	436	6.30

*(M + Na)⁺,
#TFA system,
&EI-MS(M⁺)

TABLE 3

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
23	521	5.77
		5.85
23-(A)-a	521	5.85
23-(A)-b	521	5.77
24	556**	6.08
		6.17
24-(A)-a	534	6.17
24-(A)-b	534	6.08
25	445	5.67
25-(A)-a	445	5.65
25-(A)-b	445	5.60
26	477#	5.72
27	442**	5.98
28	420**, #	5.30
29	428, 430**	5.80, 5.92
30	590**	5.60#

TABLE 3-continued

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
31	572	5.82#
32	497	5.82#
33	436, 438	6.05#
34	586**	6.31#
35	539	5.02#

*[M - H]⁻
**[M + Na]⁺
#TFA system

TABLE 4

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
36#	551	5.70
37##	484**	1.24
38##	524**	1.19
39##	572**	1.22
40##	586**	1.19
41##	586**	1.20
42##	572**	1.21
43##	484**	1.24
44#	502	6.22
45#	620**	5.87
46##	514**	1.24
47##	600**	1.21
48##	472**	1.19
49##	472**	1.19
50##	497**	1.11
51	537	5.87
		5.97
51(A)-a	537	5.87
51(A)-b	537	5.82
52	451	5.78
		5.85
52(A)-a	451	5.78
52(A)-b	451	5.70
53	456**	6.18
		6.30
53a	456**	6.27
53b	456**	6.18
54##	507	1.11
54(A)-a	507	5.92
54(A)-b	507	5.83
55##	435	0.87
55(A)-a	435	5.28
55(A)-b	435	5.23

415

TABLE 4-continued

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
56(A)-a##	428, 430**	1.13
56(A)-b##	428, 430**	1.14
57##	542**	1.18
58##	542**	1.19
59##	590**	1.09
60##	454**	1.22
61##	484**	1.20
62##	555	1.00
63##	449	1.09
64##	494**	1.16
65##	495**	1.13
66##	440**	1.19
67##	458**	1.19
68##	474**	1.13
69##	488**	1.18

#TFA system

##UPLC

*[M - H]⁻**[M + Na]⁺

TABLE 5

Example No.	Substituted Phenylboronic Ester		Substituted Isothiazole	
	ESI-MS (M + 1) ⁺	Retention Time (Minute)	ESI-MS (M + 1) ⁺	Retention Time (Minute)
1	532	5.87	492	6.08#
2	550	6.03	510	6.07#
3	586*	5.98	524	6.02#
4	546	5.95#	528*	6.05
5	581	4.32#	541	4.54#
6	547	5.62	507	4.83
7	568*	6.02	528*	6.53
8	632	6.97#	478	5.77#
9	668*	6.97#	494	5.45#
10	588	6.07#	508	5.75
11	617	6.12	577	6.57
12	574	6.15	492	6.01#
13	580	5.49	540	5.78

*(M + Na)⁺,

#TFA system

416

TABLE 7

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
23-1	296**	5.78
23-3	443*, #	5.75
23-5	519	6.08
24-1	309**	6.22
24-2	343**	5.94
24-3	532	6.46
25-3	285**	5.18
25-4	358**	6.15
25-5	234#	5.18
25-6	481*	5.57
25-7	443#	5.70
30-1	343, 345**	5.63
31-1	378**	6.52
31-2	475**	6.20
31-3	813**	7.03
31-4	944**	6.85
31-5	886**	6.87
31-6	626**	5.63
32-1	572**	7.06
32-2	704**	6.92
32-3	646**	7.03
32-4	556**	6.50
32-5	789**	7.05
33-1	—	6.13
33-2	678, 680**	7.37
33-3	808, 810**	7.24
33-4	750, 752**	7.26
35-1	650, 652**	7.23
35-2	782, 784**	7.03
35-3	724, 726**	7.10
35-4	464, 466**	5.55
35-5	432, 434**	5.78#
Reference Example 2	433, 435**	5.93

40 *[M - H]⁻**[M + Na]⁺

#TFA system

TABLE 6

No.	ESI-MS (M + 1) ⁺	Retention Time (Minute)	No.	ESI-MS (M + 1) ⁺	Retention Time (Minute)	No.	ESI-MS (M + 1) ⁺	Retention Time (Minute)
14-1	426*	6.72	14-2	304	5.57	14-3	418	6.72
14-4	619*	6.84	14-5	441	5.98			
15-1	562*	6.18	15-2	440	4.82	15-3	526	5.95
15-4	727*	6.18	15-5	605	5.70			
16-1	266*	5.05	16-2	460*	6.92	16-3	338	6.45
16-4	424	6.82	16-5	503	6.38			
17-1	246*	4.53	17-2	440*	6.65	17-3	318	5.95
17-4	404	6.68	17-5	505*	6.37			
18-1	404	6.56	18-2	605*	6.72	18-3	483	6.35
19-1	556	6.22#						
21-1	339	6.45	21-2	404	4.42	21-3	505*	6.17
22-1	358*	5.40	22-2	634	7.06	22-3	788*	6.80
22-4	730*	6.92	22-5	468	6.13			

*(M + Na)⁺,

#TFA system

TABLE 8

Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)	Example	MS-ESI (m/z) [M + H] ⁺	Retention Time (Minute)
37-1##	776**	1.66	41-3B##	604**	1.12
37-2##	762**	1.51	42-2A##	850**	1.42
37-3##	502**	1.17	42-3A##	590**	1.14
38-1##	816**	1.47	43-1A##	776**	1.61
38-2##	802**	1.39	43-2A##	762**	1.49
38-3##	542**	1.12	43-3A##	502**	1.16
39-1##	864**	1.54	44-1A##	816**	1.45
39-2##	850**	1.43	44-2A##	802**	1.38
39-3##	590**	1.15	44-3A##	542**	1.11
40-1A##	750, 752**	1.51	45-1A##	912**	1.35
40-1B##	750, 752**	1.51	45-2A##	898**	1.30
40-2A##	878**	1.46	45-3A##	638**	1.03
40-3A##	864**	1.38	46-1A##	806**	1.56
40-4A##	604**	1.12	46-2A##	792**	1.45
41-1B##	878**	1.46	46-3A##	532**	1.14
41-2B##	864**	1.39	47-1#	353, 355**	6.37
47-2##	690, 692**	1.68	50-2A##	775**	1.32
47-3##	820, 822**	1.45	50-3A##	515**	1.04
47-4##	764, 766**	1.54	51-1	344	5.50
47-5##	892**	1.48	51-2	575	5.78
47-6##	879**	1.39	51-3	535	5.90
47-7##	618**	1.14	52-1	258	5.13
48-1##	730 (Boronic acid + Na)	1.33	52-2	489	5.62
48-2##	688**	1.30	52-3#	449	5.82
48-3##	764**	1.53	53-1	223 (M - H ₂ O + 1)	5.85
48-4##	750**	1.42	53-2	494**	6.10
48-5##	490**	1.11	53-3#	454**	6.27
49-1A##	730 (Boronic acid + Na)	1.33	54-1	260, 262	5.85
49-2A##	688**	1.29	54-2##	294	0.53
49-3A##	764**	1.50	55-1	242	4.28
49-4A##	750**	1.41	55-2	473	5.20
49-5A##	490**	1.11	55-3#	433	4.38
50-1A##	789**	1.37			

#TFA system

##UPLC

*[M - H]⁻**[M + Na]⁺

TABLE 9

Example	NMR data (δ: ppm) <400 MHz (*: 300 MHz)>
1	(CDCl ₃) δ: 7.42 (1H, t, J = 8 Hz), 7.40-7.32 (1H, m), 7.20-7.13 (1H, m), 7.17 (2H, d, J = 9 Hz), 7.12-7.07 (1H, m), 6.98 (2H, d, J = 9 Hz), 6.68 (2H, s), 5.10 (2H, s), 4.41 (1H, d, J = 7 Hz), 4.13 (2H, t, J = 5 Hz), 3.80 (2H, t, J = 5 Hz), 3.62 (2H, q, J = 7 Hz), 3.55 (1H, d, J = 8 Hz), 2.91-2.84 (1H, m), 1.97 (6H, s), 1.25 (3H, t, J = 7 Hz).
12*	(CDCl ₃) δ: 7.50-7.33 (4H, m), 7.21-6.96 (4H, m), 6.68 (2H, s), 5.16-5.10 (2H, m), 4.53-4.39 (1H, m), 4.26-4.07 (3H, m), 3.70-3.52 (0.25H, m, isomer-1), 3.35-3.21 (0.75H, m, isomer-2), 3.02-2.83 (1H, m), 2.03-1.90 (2H, m), 2.00 (6H, s), 1.30 (3H, d, J = 6 Hz).
13	(DMSO-D ₆) δ: 11.00 (1H, s), 7.48-7.35 (2H, m), 7.22 (2H, d, J = 9 Hz), 7.14 (1H, s), 7.09-7.00 (3H, m), 6.70 (2H, s), 5.16 (2H, s), 4.51 (1H, d, J = 8 Hz), 4.08 (2H, t, J = 6 Hz), 3.52-3.39 (1H, m), 3.27 (2H, t, J = 8 Hz), 3.02 (3H, s), 2.80 (1H, d, J = 17 Hz), 2.19-2.08 (2H, m), 1.90 (6H, s).
14*	(DMSO-D ₆) δ: 7.50-7.37 (2H, m), 7.22-6.88 (9H, m), 5.10 (2H, s), 3.90 (2H, s), 1.95 (6H, s).
16*	(CDCl ₃) δ: 7.57-7.28 (3H, m), 7.20-6.95 (6H, m), 6.95-6.80 (1H, m), 5.07 (2H, s), 4.40 (2H, br s), 1.99 (6H, s).
17*	(CDCl ₃) δ: 7.48-7.28 (3H, m), 7.20-7.01 (5H, m), 6.89-6.77 (2H, m), 5.08 (2H, s), 4.29 (2H, br s), 2.36 (3H, s), 2.00 (6H, s).
18*	(CDCl ₃) δ: 7.50-7.31 (4H, m), 7.21-7.00 (7H, m), 5.14 (2H, s), 4.51 (1H, q, J = 7 Hz), 2.01 (6H, s), 1.45 (3H, d, J = 7 Hz).
19	(DMSO-D ₆) δ: 7.47-7.38 (2H, m), 7.20 (2H, d, J = 9 Hz), 7.16 (1H, s), 7.05 (1H, dt, J = 7, 2 Hz), 6.96 (2H, d, J = 9 Hz), 6.70 (2H, s), 5.14 (2H, s), 4.33 (1H, t, J = 8 Hz), 4.08 (2H, t, J = 6 Hz), 3.30-3.24 (1H, m), 3.02 (3H, s), 2.84 (1H, dd, J = 16, 8 Hz), 2.63 (2H, dd, J = 16, 8 Hz), 2.17-2.10 (2H, m), 1.92 (6H, s).

TABLE 9-continued

Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
21	(DMSO-D ₆) δ : 11.97 (1H, br s), 7.93 (1H, br s), 7.52-7.41 (2H, m), 7.37 (2H, d, J = 9 Hz), 7.20 (1H, s), 7.18-7.08 (4H, m), 7.03 (2H, d, J = 9 Hz), 5.19 (2H, s), 4.76-4.66 (1H, m), 2.80-2.66 (1H, m), 2.64-2.54 (1H, m), 1.95 (6H, s).
22	(CDCl ₃) δ : 7.46 (1H, t, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.22-7.08 (7H, m), 6.99 (2H, d, J = 9 Hz), 5.13 (2H, s), 3.81-3.69 (1H, m), 3.66-3.59 (1H, m), 3.45 (1H, dd, J = 14, 12 Hz), 3.03-2.92 (1H, m), 2.82 (1H, dd, J = 17, 12 Hz), 2.01 (6H, s).

TABLE 10

Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
23(A)-a	¹ H-NMR (CDCl ₃) δ : 7.47-7.27 (4H, m), 7.22 (2H, d, J = 9 Hz), 7.16 (1H, d, J = 6 Hz), 7.04 (2H, d, J = 9 Hz), 6.61 (1H, d, J = 8 Hz), 5.84-5.79 (1H, m), 4.56 (2H, t, J = 6 Hz), 4.44 (1H, d, J = 8 Hz), 3.60 (1H, dd, J = 17, 8 Hz), 2.92-2.80 (1H, m), 2.91 (1H, d, 17 Hz), 2.71-2.60 (1H, m), 2.60-2.49 (1H, m), 2.27 (3H, s), 2.19-2.09 (1H, m), 2.02 (2H, t, J = 6 Hz), 1.32 (6H, s).
23(A)-b	¹ H-NMR (CDCl ₃) δ : 7.62 (1H, s), 7.45-7.29 (5H, m), 7.16 (1H, d, J = 6 Hz), 7.09 (2H, d, J = 9 Hz), 6.61 (1H, d, J = 8 Hz), 5.86-5.82 (1H, m), 4.56 (2H, t, J = 6 Hz), 4.51 (1H, dd, J = 12, 7 Hz), 3.30 (1H, dd, J = 17, 12 Hz), 2.98 (1H, dd, J = 17, 7 Hz), 2.94-2.81 (1H, m), 2.73-2.51 (2H, m), 2.28 (3H, s), 2.21-2.11 (1H, m), 2.02 (2H, t, J = 6 Hz), 1.32 (6H, s).
25(A)-a*	¹ H-NMR (CDCl ₃) δ : 7.68 (1H, s), 7.60 (2H, d, J = 9 Hz), 7.33-7.28 (2H, m), 7.22 (2H, d, J = 9 Hz), 7.02 (2H, d, J = 9 Hz), 7.03-6.98 (1H, m), 6.97 (2H, d, J = 9 Hz), 5.79 (1H, dd, J = 7, 5 Hz), 4.44 (1H, d, J = 8 Hz), 3.60 (1H, dd, J = 18, 8 Hz), 3.01-2.88 (1H, m), 2.90 (1H, d, J = 18 Hz), 2.82-2.69 (1H, m), 2.61-2.51 (1H, m), 2.24-2.11 (1H, m).
26	¹ H-NMR (CDCl ₃) δ : 7.62 (2H, d, J = 9 Hz), 7.38-7.30 (4H, m), 7.07 (2H, d, J = 9 Hz), 7.02 (1H, dd, J = 4, 4 Hz), 6.99 (2H, d, J = 9 Hz), 5.86-5.79 (1H, m), 5.00-4.91 (1H, m), 4.65 (1H, d, J = 11 Hz), 3.09 (1H, dd, J = 17, 4 Hz), 3.03-2.91 (1H, m), 2.91 (1H, dd, J = 12, 17 Hz), 2.83-2.72 (1H, m), 2.67-2.55 (1H, m), 2.27-2.15 (1H, m).
31	¹ H-NMR (CDCl ₃) δ : 7.48-7.34 (2H, m), 7.19-7.03 (4H, m), 7.01-6.92 (2H, m), 6.64 (2H, s), 5.10 (2H, s), 4.18-4.06 (2H, m), 3.80-3.56 (2H, m), 3.53-3.37 (1H, m), 3.31-3.22 (2H, m), 3.01-2.90 (1H, m), 2.97 (3H, s), 2.86-2.71 (1H, m), 2.42-2.29 (2H, m), 1.97 (6H, s).
35	¹ H-NMR (DMSO-D ₆) δ : 7.50-7.40 (2H, m), 7.23-7.16 (3H, m), 7.15-7.10 (1H, m), 6.93 (2H, d, J = 9 Hz), 6.55 (1H, s), 5.13 (2H, s), 4.37 (1H, s), 4.33 (2H, t, J = 7 Hz), 3.26-3.15 (1H, m), 2.94-2.79 (2H, m), 2.28-2.20 (1H, m), 2.19-2.09 (1H, m), 2.06 (3H, s), 1.90 (3H, s), 1.82 (2H, t, J = 7 Hz), 1.16 (6H, s).
36	¹ H-NMR (DMSO-D ₆) δ : 7.49 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.35-7.28 (1H, m), 7.24 (2H, d, J = 9 Hz), 7.18 (1H, d, J = 6 Hz), 6.98 (2H, d, J = 9 Hz), 6.65 (1H, d, J = 8 Hz), 5.90-5.84 (1H, m), 4.39 (1H, s), 4.37 (2H, t, J = 7 Hz), 3.54-2.85 (3H, m), 2.84-2.44 (3H, m), 2.38-2.14 (2H, m), 2.21 (3H, s), 2.06-1.92 (1H, m), 1.85 (2H, t, J = 7 Hz), 1.18 (6H, s).

TABLE 11

Example	NMR data (δ : ppm) <*: 300 MHz>
40	¹ H-NMR (DMSO-D ₆) δ : 12.14 (1H, s), 7.39-7.28 (4H, m), 7.06-6.98 (3H, m), 6.70 (2H, s), 5.94-5.88 (1H, m), 4.38 (1H, s), 4.07 (2H, t, J = 7 Hz), 3.84-3.42 (3H, m), 2.84-2.62 (2H, m), 2.61-2.35 (3H, m), 2.00-1.88 (1H, m), 1.90 (3H, s), 1.87 (3H, s), 1.84 (2H, t, J = 7 Hz), 1.18 (6H, s).
42	¹ H-NMR (DMSO-D ₆) δ : 12.14 (1H, brs), 7.35-7.31 (4H, m), 7.03-7.00 (3H, m), 6.72 (2H, s), 5.92-5.90 (1H, m), 4.09-4.07 (2H, m), 3.81-3.78 (1H, m), 3.70-3.67 (3H, m), 3.59-3.55 (1H, m), 3.51 (2H, q, J = 7 Hz), 2.85-2.64 (2H, m), 2.61-2.35 (3H, m), 1.98-1.88 (1H, m), 1.90 (3H, s), 1.87 (3H, s), 1.14 (3H, t, J = 7 Hz).
44*	¹ H-NMR (DMSO-D ₆) δ : 12.12 (1H, s), 7.85 (1H, d, J = 8 Hz), 7.73 (1H, dd, J = 7, 7 Hz), 7.66-7.58 (1H, m), 7.47-7.26 (5H, m), 7.16 (1H, d, J = 7 Hz), 7.03 (2H, d, J = 8 Hz), 5.95-5.87 (1H, m), 3.79-3.45 (3H, m), 2.83-2.35 (5H, m), 2.04-1.85 (1H, m).
47	¹ H-NMR (*DMSO-D ₆) δ : 12.07 (1H, s), 7.39-7.22 (3H, m), 7.03-6.96 (1H, m), 6.94-6.85 (2H, m), 6.69 (2H, s), 5.93-5.85 (1H, m), 4.35 (1H, s), 4.07 (2H, t, J = 7 Hz), 3.77-3.43 (3H, m), 2.86-2.22 (5H, m), 2.31 (3H, s), 1.97-1.77 (3H, m), 1.90 (3H, s), 1.87 (3H, s), 1.18 (6H, s).
48	¹ H-NMR (DMSO-D ₆) δ : 7.44-6.85 (12H, m), 5.85 (1H, dd, J = 6, 4 Hz), 3.30-2.46 (5H, m), 2.37-1.93 (4H, m).
51(A)-a	¹ H-NMR (DMSO-D ₆) δ : 7.35 (1H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.20-7.14 (1H, m), 7.12-7.03 (3H, m), 6.65 (1H, d, J = 9 Hz), 6.52 (1H, d, J = 8 Hz), 5.89 (1H, dd, J = 7, 4 Hz), 4.50 (1H, d, J = 8 Hz), 4.38 (1H, s), 4.32 (2H, t, J = 7 Hz), 3.55-3.20 (1H, m), 3.06-2.93 (1H, m), 2.92-2.74 (2H, m), 2.70-2.55 (1H, m), 2.27 (3H, s), 2.10-1.98 (1H, m), 1.83 (2H, t, J = 7 Hz), 1.17 (6H, s).

TABLE 11-continued

Example	NMR data (δ : ppm) <*: 300 MHz>
51(A)-b	¹ H-NMR (DMSO-D ₆) δ : 7.41 (2H, d, J = 9 Hz), 7.36 (1H, d, J = 9 Hz), 7.22-7.15 (1H, m), 7.11 (1H, d, J = 7 Hz), 7.07 (2H, d, J = 9 Hz), 6.65 (1H, d, J = 9 Hz), 6.53 (1H, d, J = 8 Hz), 5.92 (1H, dd, J = 7, 4 Hz), 4.79-4.69 (1H, m), 4.38 (1H, s), 4.32 (2H, t, J = 7 Hz), 3.53-2.39 (5H, m), 2.27 (3H, s), 2.11-2.00 (1H, m), 1.83 (2H, t, J = 7 Hz), 1.17 (6H, s).
54(A)-a	¹ H-NMR (DMSO-D ₆) δ : 11.05 (1H, s), 7.51 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.32 (1H, t, J = 7 Hz), 7.27 (2H, d, J = 9 Hz), 7.21-7.17 (1H, m), 7.10 (2H, d, J = 9 Hz), 6.70 (1H, d, J = 8 Hz), 5.94-5.89 (1H, m), 4.54 (1H, d, J = 8 Hz), 4.39 (2H, t, J = 5 Hz), 3.71 (2H, t, J = 5 Hz), 3.54-3.40 (1H, m), 3.50 (2H, q, J = 7 Hz), 2.82 (1H, d, J = 17 Hz), 2.82-2.43 (3H, m), 2.20 (3H, s), 2.03-1.90 (1H, m), 1.13 (3H, t, J = 7 Hz).
56(A)-a	¹ H-NMR (CDCl ₃) δ : 7.89 (1H, s), 7.48 (1H, d, J = 8 Hz), 7.42-7.33 (3H, m), 7.17-7.10 (1H, m), 7.07-7.02 (2H, m), 5.83 (1H, dd, J = 7, 5 Hz), 4.50 (1H, dd, J = 12, 7 Hz), 3.29 (1H, dd, J = 17, 12 Hz), 3.21-3.09 (1H, m), 3.03-2.89 (2H, m), 2.66-2.53 (1H, m), 2.28-2.15 (1H, m).
56(A)-b	¹ H-NMR (CDCl ₃) δ : 7.48 (1H, d, J = 8 Hz), 7.33 (1H, d, J = 7 Hz), 7.21 (2H, d, J = 9 Hz), 7.17-7.09 (1H, m), 7.00 (2H, d, J = 9 Hz), 5.81 (1H, dd, J = 7, 4 Hz), 4.43 (1H, d, J = 8 Hz), 3.60 (1H, dd, J = 18, 8 Hz), 3.23-3.08 (1H, m), 3.02-2.82 (2H, m), 2.64-2.51 (1H, m), 2.25-2.13 (1H, m).
57	¹ H-NMR (DMSO-D ₆) δ : 11.10 (1H, s), 7.42 (2H, d, J = 9 Hz), 7.39-7.28 (2H, m), 7.09 (2H, d, J = 9 Hz), 7.03-6.99 (1H, m), 6.72 (2H, s), 5.99-5.92 (1H, m), 4.79 (1H, dd, J = 12, 7 Hz), 4.10-4.05 (2H, m), 3.73-3.66 (2H, m), 3.51 (2H, q, J = 7 Hz), 3.23 (1H, dd, J = 17, 12 Hz), 2.86 (1H, dd, J = 17, 8 Hz), 2.63-2.36 (3H, m), 2.01-1.89 (1H, m), 1.91 (3H, s), 1.87 (3H, s), 1.14 (3H, t, J = 7 Hz).
58	¹ H-NMR (DMSO-D ₆) δ : 11.04 (1H, s), 7.38-7.28 (2H, m), 7.26 (2H, d, J = 9 Hz), 7.10 (2H, d, J = 9 Hz), 7.00 (1H, d, J = 7 Hz), 6.72 (2H, s), 5.96-5.90 (1H, m), 4.54 (1H, d, J = 8 Hz), 4.08 (2H, t, J = 5 Hz), 3.69 (2H, t, J = 5 Hz), 3.51 (2H, q, J = 7 Hz), 3.35-3.27 (1H, m), 2.82 (1H, d, J = 17 Hz), 2.62-2.37 (3H, m), 1.99-1.88 (1H, m), 1.90 (3H, s), 1.87 (3H, s), 1.14 (3H, t, J = 7 Hz).
59*	¹ H-NMR (DMSO-D ₆) δ : 11.01 (1H, s), 7.39-7.29 (2H, m), 7.26 (2H, d, J = 9 Hz), 7.10 (2H, d, J = 9 Hz), 7.00 (1H, dd, J = 7, 2 Hz), 6.72 (2H, s), 5.98-5.88 (1H, m), 4.53 (1H, d, J = 8 Hz), 4.09 (2H, t, J = 6 Hz), 3.52-3.38 (1H, m), 3.37-3.28 (1H, m), 3.34-3.28 (2H, m), 3.30-3.23 (1H, m), 3.03 (3H, s), 2.87-2.76 (1H, m), 2.63-2.50 (1H, m), 2.48-2.34 (1H, m), 2.21-2.07 (2H, m), 1.95-1.82 (6H, m).
64	¹ H-NMR (CDCl ₃) δ : 7.80-7.72 (1H, m), 7.59-7.53 (1H, m), 7.53-7.38 (3H, m), 7.34-7.23 (2H, m), 7.24-7.17 (2H, m), 7.04 (2H, d, J = 9 Hz), 5.87-5.77 (1H, m), 4.44 (1H, d, J = 8 Hz), 3.60 (1H, dd, J = 18, 8 Hz), 2.94-2.88 (1H, m), 2.91-2.63 (2H, m), 2.63-2.45 (1H, m), 2.21-2.05 (1H, m).
68	¹ H-NMR (CDCl ₃) δ : 7.48-7.41 (1H, m), 7.36-7.28 (2H, m), 7.21 (2H, d, J = 9 Hz), 7.15-7.08 (1H, m), 7.05 (2H, d, J = 9 Hz), 7.02-6.94 (1H, m), 6.91-6.83 (1H, m), 5.86-5.78 (1H, m), 4.44 (1H, d, J = 7 Hz), 3.93 (3H, s), 3.59 (1H, dd, J = 18, 8 Hz), 3.08-2.97 (1H, m), 2.96-2.80 (2H, m), 2.62-2.49 (1H, m), 2.23-2.08 (1H, m).

TABLE 12

Substituted Isothiazole	
Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
1-6	(DMSO-D ₆) δ : 11.27 (1H, s), 7.80 (2H, d, J = 9 Hz), 7.51-7.40 (2H, m), 7.24-7.16 (3H, m), 7.08 (1H, d, J = 7 Hz), 7.07 (1H, s), 6.71 (2H, s), 5.27 (2H, s), 4.10-4.05 (2H, m), 3.72-3.66 (2H, m), 3.51 (2H, q, J = 7 Hz), 1.92 (6H, s), 1.14 (3H, t, J = 7 Hz)
12-5	(DMSO-D ₆) δ : 11.28 (1H, s), 7.83-7.76 (2H, m), 7.50-7.39 (2H, m), 7.24-7.16 (3H, m), 7.08 (2H, d, J = 9 Hz), 6.68 (2H, s), 5.26 (2H, s), 4.58-4.53 (1H, m), 4.09-3.95 (2H, m), 3.87-3.74 (1H, m), 1.91 (6H, s), 1.81-1.68 (2H, m), 1.15-1.08 (3H, m)
13-5	(DMSO-D ₆) δ : 7.79 (2H, d, J = 9 Hz), 7.50-7.39 (2H, m), 7.23-7.16 (3H, m), 7.11-7.03 (2H, m), 6.71 (2H, s), 5.26 (2H, s), 4.08 (2H, t, J = 6 Hz), 3.31-3.24 (2H, m), 3.03 (3H, s), 2.19-2.09 (2H, m), 1.92 (6H, s)

TABLE 13

Substituted Boronic Ester	
Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
1-3	(CDCl ₃) δ : 7.45-7.35 (4H, m), 7.18 (1H, s), 7.11-7.06 (1H, m), 6.99 (2H, d, J = 9 Hz), 6.69 (2H, s), 5.11 (2H, s), 4.16-4.12 (2H, m), 3.95 (2H, d, J = 16 Hz), 3.80 (2H, t, J = 5 Hz), 3.75 (2H, d, J = 16 Hz),

TABLE 13-continued

Substituted Boronic Ester	
Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
12-4	3.62 (2H, q, J = 7 Hz), 2.53 (3H, s), 1.98 (6H, s), 1.25 (3H, t, J = 7 Hz) (CDCl ₃) δ : 7.47-7.35 (4H, m), 7.17 (1H, s), 7.08 (1H, d, J = 7 Hz), 6.99 (2H, d, J = 9 Hz), 6.63 (2H, s), 5.20-5.06 (2H, m), 5.12 (1H, s), 4.01 (2H, t, J = 6 Hz), 3.89 (2H, d, J = 16 Hz), 3.74 (2H, d, J = 16 Hz), 2.54 (3H, s), 2.12-1.99 (2H, m), 2.05 (3H, s), 1.98 (6H, s), 1.32 (3H, d, J = 6 Hz)
13-4*	(DMSO-D ₆) δ : 7.50-7.37 (2H, m), 7.33 (2H, d, J = 9 Hz), 7.16 (1H, s), 7.10-7.02 (1H, m), 6.99 (2H, d, J = 9 Hz), 6.70 (2H, s), 5.16 (2H, s), 4.30 (2H, d, J = 17 Hz), 4.14-3.97 (4H, m), 3.31-3.22 (2H, m), 3.03 (3H, s), 2.47 (3H, s), 2.20-2.07 (2H, m), 1.91 (6H, s)

TABLE 14

Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
14-3	(CDCl ₃) δ : 7.46-7.36 (2H, m), 7.21-7.12 (2H, m), 7.12-7.05 (3H, m), 6.84 (2H, d, J = 9 Hz), 6.55 (2H, d, J = 9 Hz), 5.03 (2H, s), 4.01 (1H, br s), 3.75 (2H, s), 2.01 (6H, s), 1.47 (9H, s).
14-5*	(CDCl ₃) δ : 7.49-7.32 (4H, m), 7.22-7.05 (5H, m), 6.96 (2H, d, J = 9 Hz), 5.11 (2H, s), 5.00 (2H, br s), 4.45 (2H, s), 2.01 (6H, s).
18-3*	(CDCl ₃) δ : 7.49-7.28 (4H, m), 7.22-7.04 (5H, m), 7.00-6.91 (2H, m), 5.11 (2H, s), 4.95 (1H, q, J = 8 Hz), 4.25 (2H, q, J = 7 Hz), 2.01 (6H, s), 1.31 (3H, t, J = 7 Hz), 1.23 (4H, d, J = 8 Hz).
21-2*	(CDCl ₃) δ : 7.49-7.36 (2H, m), 7.27 (2H, d, J = 9 Hz), 7.22-7.06 (5H, m), 6.94 (2H, d, J = 9 Hz), 5.10 (2H, s), 4.38 (1H, dd, J = 8, 6 Hz), 4.13 (2H, q, J = 7 Hz), 2.70-2.59 (2H, m), 2.01 (6H, s), 1.23 (3H, t, J = 7 Hz).
22-3*	(CDCl ₃) δ : 7.49-7.37 (2H, m), 7.24-7.06 (11H, m), 6.90 (2H, d, J = 9 Hz), 6.83 (4H, d, J = 9 Hz), 5.08 (2H, s), 4.22 (2H, d, J = 15 Hz), 4.03-3.96 (1H, m), 4.03 (2H, d, J = 15 Hz), 3.85 (1H, d, J = 8 Hz), 3.80 (6H, s), 3.70 (3H, s), 3.62-3.51 (1H, m), 3.55 (3H, s), 3.32 (1H, dd, J = 14, 8 Hz), 2.03 (6H, s).
22-4*	(CDCl ₃) δ : 7.51-7.37 (2H, m), 7.24-7.14 (6H, m), 7.14-7.08 (3H, m), 7.03 (2H, d, J = 9 Hz), 6.90 (2H, d, J = 9 Hz), 6.85 (4H, d, J = 9 Hz), 5.09 (2H, s), 4.31 (2H, d, J = 15 Hz), 4.11 (2H, d, J = 15 Hz), 3.81 (6H, s), 3.76-3.63 (1H, m), 3.56 (3H, s), 3.25 (1H, dd, J = 14, 8 Hz), 3.10 (1H, t, J = 5 Hz), 3.05 (1H, dd, J = 5, 2 Hz), 2.69 (1H, dd, J = 16, 9 Hz), 2.02 (6H, s).
22-5	(CDCl ₃) δ : 7.46 (1H, t, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 7.23-7.15 (4H, m), 7.15-7.08 (3H, m), 6.96 (2H, d, J = 7 Hz), 5.10 (2H, s), 4.23 (2H, br s), 3.82-3.71 (1H, m), 3.63 (3H, s), 3.54 (1H, dd, J = 14, 7 Hz), 3.39 (1H, dd, J = 14, 8 Hz), 2.94 (1H, dd, J = 16, 7 Hz), 2.73 (1H, dd, J = 16, 7 Hz), 2.02 (6H, s).

TABLE 15

Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
23-2*	¹ H-NMR (CDCl ₃) δ : 7.92 (1H, d, J = 8 Hz), 6.51 (1H, d, J = 8 Hz), 4.55 (2H, t, J = 6 Hz), 3.77 (4H, s), 2.64 (3H, s), 1.98 (2H, t, J = 6 Hz), 1.29 (6H, s), 1.03 (6H, s).
23-4	¹ H-NMR (DMSO-d ₆) 11.28 (1H, s), 7.83 (2H, d, J = 9 Hz), 7.57 (1H, d, J = 8 Hz), 7.46-7.41 (1H, m), 7.27-7.19 (1H, m), 7.23 (2H, d, J = 9 Hz), 7.11 (1H, s), 6.10 (1H, dd, J = 7, 4 Hz), 3.11-2.97 (1H, m), 2.97-2.83 (1H, m), 2.71-2.58 (1H, m), 2.15-2.00 (1H, m)
25-1	¹ H-NMR (CDCl ₃) δ : 7.42-7.38 (3H, m), 7.28 (1H, d, J = 8 Hz), 7.09 (2H, dt, J = 14, 6 Hz), 5.37 (1H, t, J = 6 Hz), 5.21 (1H, dd, J = 7, 5 Hz), 4.86-4.81 (2H, m), 4.03-3.93 (2H, m), 3.63-3.54 (2H, m), 3.13-3.03 (2H, m), 2.86-2.77 (2H, m), 2.49-2.38 (2H, m), 2.21-2.13 (1H, m), 2.06-1.98 (1H, m), 1.91-1.78 (2H, m), 1.78-1.68 (2H, m), 1.68-1.47 (8H, m).
25-2	¹ H-NMR (CDCl ₃) δ : 7.72-7.68 (2H, m), 7.52 (1H, d, J = 7 Hz), 7.40 (1H, d, J = 8 Hz), 7.24-7.16 (2H, m), 5.29 (1H, t, J = 6 Hz), 5.13 (1H, dd, J = 7, 5 Hz), 4.87 (1H, t, J = 4 Hz), 4.83 (1H, dd, J = 5, 3 Hz), 4.08-3.94 (2H, m), 3.75 (4H, s), 3.75 (4H, s), 3.62-3.54 (2H, m), 3.33-3.22 (2H, m), 3.04-2.94 (2H, m), 2.42-2.32 (2H, m), 2.16-2.07 (1H, m), 1.75-1.52 (13H, m), 1.02 (6H, s), 1.01 (6H, s).
26-1*	¹ H-NMR (DMSO-d ₆) δ : 9.84 (1H, d, J = 9 Hz), 9.42 (1H, s), 7.14 (2H, d, J = 8 Hz), 6.70 (2H, d, J = 8 Hz), 5.17 (1H, ddd, J = 9 Hz, 9 Hz, 6 Hz), 4.09-3.98 (2H, m), 2.92 (1H, dd, J = 16 Hz, 9 Hz), 2.80 (1H, dd, J = 16 Hz, 6 Hz), 1.12 (3H, t, J = 7 Hz).

TABLE 15-continued

Example	NMR data (δ : ppm) <400 MHz (*: 300 MHz)>
26-2*	¹ H-NMR (CDCl ₃) δ : 7.71 (1H, d, J = 9 Hz), 7.61 (2H, d, J = 9 Hz), 7.35-7.30 (2H, m), 7.26 (2H, d, J = 9 Hz), 7.04-6.95 (5H, m), 5.79 (1H, dd, J = 7 Hz, 4 Hz), 5.45-5.35 (1H, m), 4.15 (2H, q, J = 7 Hz), 3.04-2.86 (3H, m), 2.83-2.68 (1H, m), 2.66-2.51 (1H, m), 2.29-2.12 (1H, m), 1.23 (3H, t, J = 7 Hz).
26-3*	¹ H-NMR (CD ₃ OD) δ : 7.69 (2H, d, J = 9 Hz), 7.35-7.28 (4H, m), 7.06-6.96 (5H, m), 5.85 (1H, dd, J = 7 Hz, 4 Hz), 4.29 (1H, dd, J = 7 Hz, 8 Hz), 4.09 (2H, q, J = 7 Hz), 2.95-2.81 (1H, m), 2.80-2.50 (4H, m), 2.18-2.04 (1H, m), 1.20 (3H, t, J = 7 Hz).
26-4*	¹ H-NMR (CDCl ₃) δ : 7.61 (2H, d, J = 9 Hz), 7.37-7.30 (4H, m), 7.06-6.95 (5H, m), 5.79 (1H, dd, J = 7 Hz, 4 Hz), 5.48 (1H, d, J = 7 Hz), 4.94-4.84 (1H, m), 4.43 (2H, s), 4.13 (2H, q, J = 7 Hz), 3.03-2.84 (3H, m), 2.83-2.68 (1H, m), 2.66-2.50 (1H, m), 2.27-2.12 (1H, m), 1.24 (3H, t, J = 7 Hz).
30-2	¹ H-NMR (CDCl ₃) δ : 6.48 (2H, s), 4.07 (2H, t, J = 6 Hz), 3.77 (4H, s), 3.28-3.18 (2H, m), 2.93 (3H, s), 2.36 (6H, s), 2.36-2.24 (2H, m), 1.09 (6H, s).
33-1	¹ H-NMR (CDCl ₃) δ : 9.90 (1H, s), 7.87 (2H, d, J = 9 Hz), 7.50 (1H, d, J = 8 Hz), 7.37 (1H, d, J = 8 Hz), 7.15 (1H, t, J = 8 Hz), 7.09 (2H, d, J = 9 Hz), 5.96-5.89 (1H, m), 3.23-3.12 (1H, m), 3.03-2.92 (1H, m), 2.70-2.59 (1H, m), 2.29-2.18 (1H, m).
35-5	¹ H-NMR (DMSO-D ₆) δ : 12.15 (1H, s), 7.64 (1H, s), 7.52 (1H, d, J = 8 Hz), 7.44 (1H, d, J = 8 Hz), 7.35 (1H, t, J = 8 Hz), 7.30 (2H, d, J = 9 Hz), 6.98 (2H, d, J = 9 Hz), 5.11 (2H, s), 3.84-3.73 (1H, m), 3.73-3.62 (1H, m), 3.62-3.49 (1H, m), 2.82-2.71 (1H, m), 2.71-2.60 (1H, m).

TABLE 16

Example	NMR data (δ : ppm) <*: 300 MHz>
40-1A	¹ H-NMR (CDCl ₃) δ : 7.46 (1H, d, J = 8 Hz), 7.32 (1H, d, J = 7 Hz), 7.16 (2H, d, J = 9 Hz), 7.14-7.08 (1H, m), 6.91 (2H, d, J = 9 Hz), 5.76 (1H, dd, J = 7, 4 Hz), 4.71 (2H, d, J = 10 Hz), 4.67 (2H, d, J = 10 Hz), 3.82-3.72 (1H, m), 3.61-3.33 (9H, m), 3.18-3.03 (2H, m), 2.97-2.87 (1H, m), 2.72 (1H, dd, J = 16, 9 Hz), 2.62-2.50 (1H, m), 2.25-2.14 (1H, m), 0.93-0.84 (4H, m), 0.00 (18H, s).
40-1B	¹ H-NMR (CDCl ₃) δ : 7.46 (1H, d, J = 8 Hz), 7.33 (1H, d, J = 8 Hz), 7.16 (2H, d, J = 9 Hz), 7.14-7.08 (1H, m), 6.91 (2H, d, J = 9 Hz), 5.76 (1H, dd, J = 7, 4 Hz), 4.72 (2H, d, J = 10 Hz), 4.67 (2H, d, J = 10 Hz), 3.82-3.69 (1H, m), 3.62-3.32 (9H, m), 3.19-3.04 (2H, m), 2.98-2.87 (1H, m), 2.72 (1H, dd, J = 16, 9 Hz), 2.61-2.50 (1H, m), 2.24-2.13 (1H, m), 0.95-0.83 (4H, m), 0.00 (18H, s).
40-2A	¹ H-NMR (CDCl ₃) δ : 7.40 (1H, d, J = 7 Hz), 7.34-7.28 (1H, m), 7.18 (2H, d, J = 9 Hz), 7.05 (1H, d, J = 6 Hz), 6.97 (2H, d, J = 9 Hz), 6.69 (2H, s), 5.82-5.77 (1H, m), 4.75-4.65 (4H, m), 4.21 (2H, t, J = 6 Hz), 3.83-3.71 (1H, m), 3.63-3.34 (9H, m), 3.11 (1H, dd, J = 16, 5 Hz), 2.79-2.63 (2H, m), 2.59-2.43 (3H, m), 2.17-2.07 (1H, m), 2.02 (2H, t, J = 6 Hz), 1.98 (3H, s), 1.95 (3H, s), 1.34 (6H, s), 0.95-0.86 (4H, m), 0.01 (18H, s).
40-3A	¹ H-NMR (CDCl ₃) δ : 7.38 (1H, d, J = 7 Hz), 7.31-7.27 (1H, m), 7.18 (2H, d, J = 9 Hz), 7.03 (1H, d, J = 7 Hz), 6.96 (2H, d, J = 9 Hz), 6.67 (2H, s), 5.81-5.76 (1H, m), 4.72 (2H, d, J = 10 Hz), 4.67 (2H, d, J = 10 Hz), 4.20 (2H, t, J = 6 Hz), 3.82-3.70 (1H, m), 3.62-3.32 (6H, m), 3.18 (1H, dd, J = 16, 5 Hz), 2.77 (1H, dd, J = 16, 10 Hz), 2.72-2.61 (1H, m), 2.59-2.41 (2H, m), 2.16-2.07 (1H, m), 2.01 (2H, t, J = 6 Hz), 1.97 (3H, s), 1.93 (3H, s), 0.92-0.86 (4H, m), 0.00 (25H, s).
40-4A	¹ H-NMR (CDCl ₃) δ : 7.39 (1H, d, J = 7 Hz), 7.34-7.27 (1H, m), 7.23 (2H, d, J = 9 Hz), 7.06-7.03 (1H, m), 7.01 (2H, d, J = 9 Hz), 6.68 (2H, s), 5.84-5.76 (1H, m), 4.36 (2H, s), 4.20 (2H, t, J = 6 Hz), 3.83-3.70 (1H, m), 3.58 (1H, dd, J = 15, 7 Hz), 3.45-3.37 (1H, m), 3.01 (1H, dd, J = 16, 7 Hz), 2.85-2.75 (1H, m), 2.74-2.62 (1H, m), 2.60-2.41 (1H, m), 2.16-2.07 (1H, m), 2.03-1.98 (2H, m), 1.97 (3H, s), 1.94 (3H, s), 1.33 (6H, s).
48-1	¹ H-NMR (CDCl ₃) δ : 7.78-7.74 (1H, m), 7.45 (1H, d, J = 7 Hz), 7.25-7.20 (1H, m), 7.15 (2H, d, J = 9 Hz), 6.93 (2H, d, J = 9 Hz), 5.68 (1H, dd, J = 7, 4 Hz), 4.72 (2H, d, J = 10 Hz), 4.67 (2H, d, J = 10 Hz), 3.80-3.70 (1H, m), 3.76 (4H, s), 3.62-3.25 (10H, m), 3.17-3.04 (2H, m), 2.72 (1H, dd, J = 16, 9 Hz), 2.56-2.43 (1H, m), 2.19-2.07 (1H, m), 1.02 (6H, s), 0.93-0.84 (4H, m), 0.00 (18H, s).
48-2	¹ H-NMR (CDCl ₃) δ : 7.18-7.11 (1H, m), 7.15 (2H, d, J = 9 Hz), 7.00 (1H, d, J = 8 Hz), 6.92 (2H, d, J = 9 Hz), 6.75 (1H, d, J = 8 Hz), 5.71 (1H, dd, J = 6, 4 Hz), 4.75-4.63 (4H, m), 3.81-3.69 (1H, m), 3.61-3.34 (9H, m), 3.13-2.99 (2H, m), 2.90-2.79 (1H, m), 2.72 (1H, dd, J = 16, 9 Hz), 2.62-2.50 (1H, m), 2.27-2.16 (1H, m), 0.93-0.84 (4H, m), 0.00 (18H, s).
48-3	¹ H-NMR (CDCl ₃) δ : 7.36-6.85 (12H, m), 5.75 (1H, dd, J = 7, 4 Hz), 4.74-4.64 (4H, m), 3.82-3.71 (1H, m), 3.62-3.33 (9H, m), 3.14-2.96 (2H, m), 2.86-2.77 (1H, m), 2.73 (1H, dd, J = 16, 10 Hz), 2.60-2.49 (1H, m), 2.23-2.11 (1H, m), 0.94-0.84 (4H, m), 0.00 (18H, s).
48-4	¹ H-NMR (CDCl ₃) δ : 7.37-6.85 (12H, m), 5.75 (1H, dd, J = 7, 5 Hz), 4.74-4.65 (4H, m), 3.81-3.71 (1H, m), 3.61-3.32 (6H, m), 3.18 (1H, dd, J = 16, 5 Hz), 3.07-2.95 (1H, m), 2.87-2.72 (2H, m), 2.61-2.49 (1H, m), 2.24-2.11 (1H, m), 0.96-0.84 (4H, m), 0.00 (18H, s).
48-5	¹ H-NMR (DMSO-D ₆) δ : 7.41-6.61 (12H, m), 6.82 (1H, s), 6.76 (1H, s), 5.86-5.81 (1H, m), 3.69-1.91 (9H, m).
51-1	¹ H-NMR (*CDCl ₃) δ : 7.20-7.08 (3H, m), 6.58-6.45 (2H, m), 5.35-5.24 (1H, m), 4.50 (2H, t, J = 6 Hz), 3.14-2.99 (1H, m), 2.87-2.66 (2H, m), 2.61-2.45 (1H, m), 2.35 (3H, s), 2.06-1.93 (3H, m), 1.31 (6H, s).
51-2	¹ H-NMR (*CDCl ₃) δ : 7.47 (2H, d, J = 9 Hz), 7.22-7.10 (3H, m), 7.04 (2H, d, J = 9 Hz), 6.59-6.50 (2H, m), 5.82 (1H, dd, J = 7, 4 Hz), 4.51 (2H, t, J = 6 Hz), 3.90 (2H, d, J = 16 Hz), 3.76 (2H, d, J = 16 Hz), 3.21-3.06 (1H, m), 3.01-2.87 (1H, m), 2.72-2.52 (1H, m), 2.59 (3H, s), 2.36 (3H, s), 2.30-2.21 (1H, m), 2.00 (2H, t, J = 6 Hz), 1.31 (6H, s).

TABLE 16-continued

Example	NMR data (δ : ppm) <*: 300 MHz>
51-3	¹ H-NMR (*DMSO-D ₆) δ : 11.28 (1H, s), 7.83 (2H, d, J = 9 Hz), 7.36 (1H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz), 7.21-7.10 (2H, m), 7.08 (1H, s), 6.66 (1H, d, J = 9 Hz), 6.59-6.50 (1H, m), 6.04 (1H, dd, J = 7, 4 Hz), 4.39 (1H, s), 4.33 (2H, t, J = 7 Hz), 3.11-2.59 (3H, m), 2.28 (3H, s), 2.17-2.01 (1H, m), 1.84 (2H, t, J = 7 Hz), 1.17 (6H, s).

The invention claimed is:

1. A compound selected from the following compound group:

- 5-[4-[[3-(2,6-dimethylphenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one;
- 5-[4-[[3-(2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl)phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one;
- 4-(((1R)-1-(4-(1,1-dioxo-3-oxo-1,2-thiazinan-5-yl)phenoxy)-2,3-dihydro-1H-inden-4-yl)oxy)benzonitrile;
- 5-(4-(((R)-4-bromo-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one;
- 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,1-dioxo-1,2-thiazinan-3-one;
- 5-[4-[[3-[6-(3-hydroxy-3-methylbutoxy)-2,4-dimethylpyridin-3-yl]phenyl]methoxy]phenyl]-1,1-dioxo-1,2-thiazinan-3-one
- 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-methoxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)-2-methylphenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-phenoxy-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

2. A compound selected from the following compound group:

- 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;
- 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;

- 10 5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide;

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 15 3. 5-(4-(((R)-4-(6-(3-hydroxy-3-methylbutoxy)-2-methylpyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide,

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 20 4. 5-(4-(((R)-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide,

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 25 5. 5-(4-(((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide,

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 30 6. 5-(4-(((R)-4-(2-(trifluoromethyl)phenyl)-2,3-dihydro-1H-inden-1-yl)oxy)phenyl)-1,2-thiazinan-3-one 1,1-dioxide,

or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 40 7. A pharmaceutical composition comprising: the compound as claimed in any one of claims 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

- 45 8. A pharmaceutical composition, characterized by comprising:

the compound as claimed in claim 1, or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer; and

one or more compounds selected from the group consisting of a PPAR gamma agonist, a biguanide agent, a sulfonylurea, a rapid-acting insulin secretagogue, an alpha-glucosidase inhibitor, insulin or an insulin derivative, GLP-1 or a GLP-1 agonist, a DPP-IV inhibitor, an alpha-2 antagonist, an SGLT2 inhibitor, an omega-3 fatty acid, an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a cholesterol absorption inhibitor, an acyl-CoA-cholesterol acyltransferase (ACAT) inhibitor, a CETP inhibitor, a squalene synthase inhibitor, an antioxidant, a PPAR alpha agonist, a PPAR delta agonist, an LXR agonist, an FXR agonist, an MTTP inhibitor, a squalene epoxidase inhibitor, a bile acid absorption inhibitor, a CB-1 receptor antagonist, a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, a lipase inhibitor, a neuropeptide Y (NPY)

429

receptor antagonist, a peptide YY (PYY) receptor antagonist, and an adrenergic beta-3 receptor agonist.

9. The pharmaceutical composition according to claim 8, wherein the DPP-IV inhibitor is a compound selected from sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and teneligliptin, or a pharmaceutically acceptable salt of the compound.

10. The pharmaceutical composition according to claim 8, wherein the DPP-IV inhibitor is sitagliptin or a pharmaceutically acceptable salt of sitagliptin.

11. A method for treating diabetes, comprising:

administering to a patient an effective amount of the compound as claimed in any one of claim 1, 2, 3, 4, 5, or 6, or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer.

12. A method for treating diabetes, comprising:

administering to a patient an effective amount of the compound as claimed in claim 1, or a pharmaceutically acceptable salt of the compound, an optical isomer of the compound, or a pharmaceutically acceptable salt of the isomer; and

one or more compounds selected from the group consisting of a PPAR gamma agonist, a biguanide agent, a sulfo-

430

nylurea, a rapid-acting insulin secretagogue, an alpha-glucosidase inhibitor, insulin or an insulin derivative, GLP-1 or a GLP-1 agonist, a DPP-IV inhibitor, an alpha-2 antagonist, an SGLT2 inhibitor, an omega-3 fatty acid, an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a cholesterol absorption inhibitor, an acyl-CoA-cholesterol acyltransferase (ACAT) inhibitor, a CETP inhibitor, a squalene synthase inhibitor, an antioxidant, a PPAR alpha agonist, a PPAR delta agonist, an LXR agonist, an FXR agonist, an MTTP inhibitor, a squalene epoxidase inhibitor, a bile acid absorption inhibitor, a CB-1 receptor antagonist, a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, a lipase inhibitor, a neuropeptide Y (NPY) receptor antagonist, a peptide YY (PYY) receptor antagonist, and an adrenergic beta-3 receptor agonist.

13. The method of claim 12, wherein the DPP-IV inhibitor is a compound selected from sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and teneligliptin, or a pharmaceutically acceptable salt of the compound.

14. The method of claim 12, wherein the DPP-IV inhibitor is sitagliptin or a pharmaceutically acceptable salt of sitagliptin.

* * * * *